Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

NOVEMBER—1955
Volume 5 — Number 11

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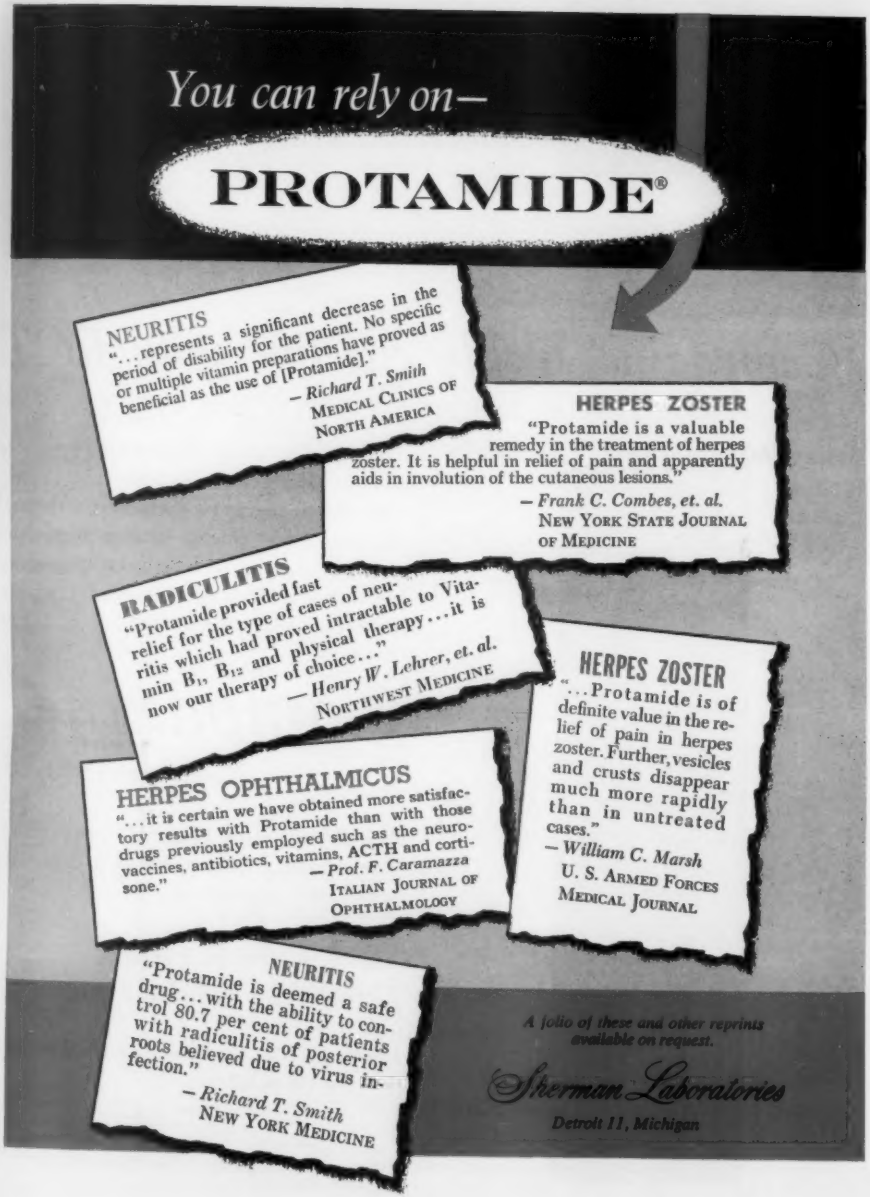
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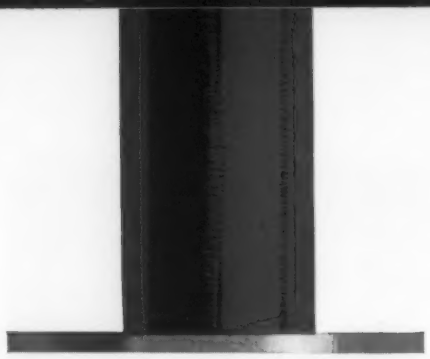

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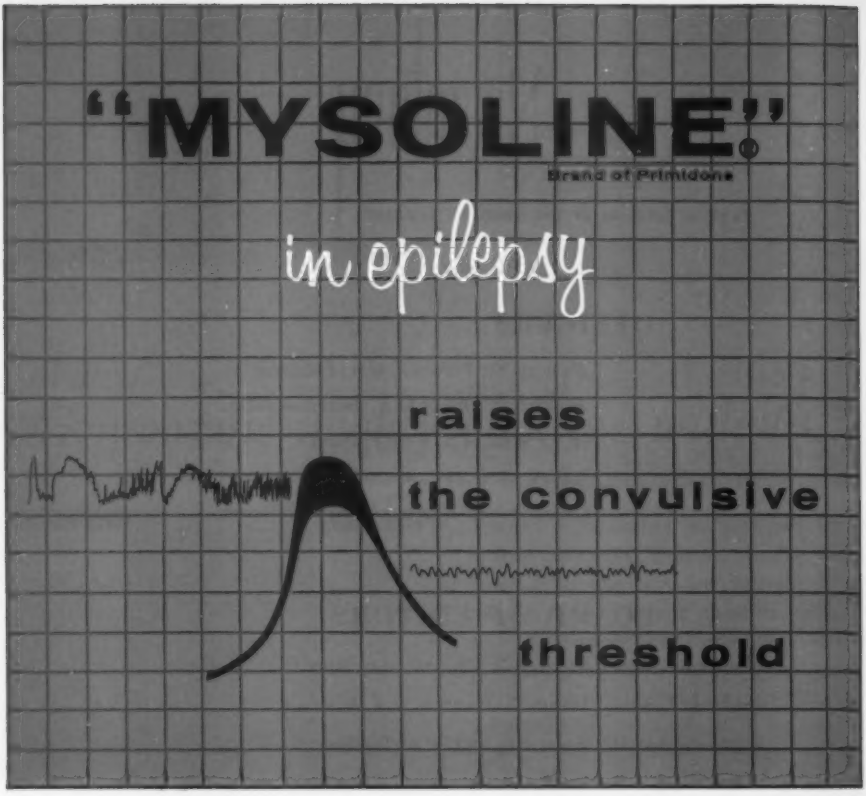

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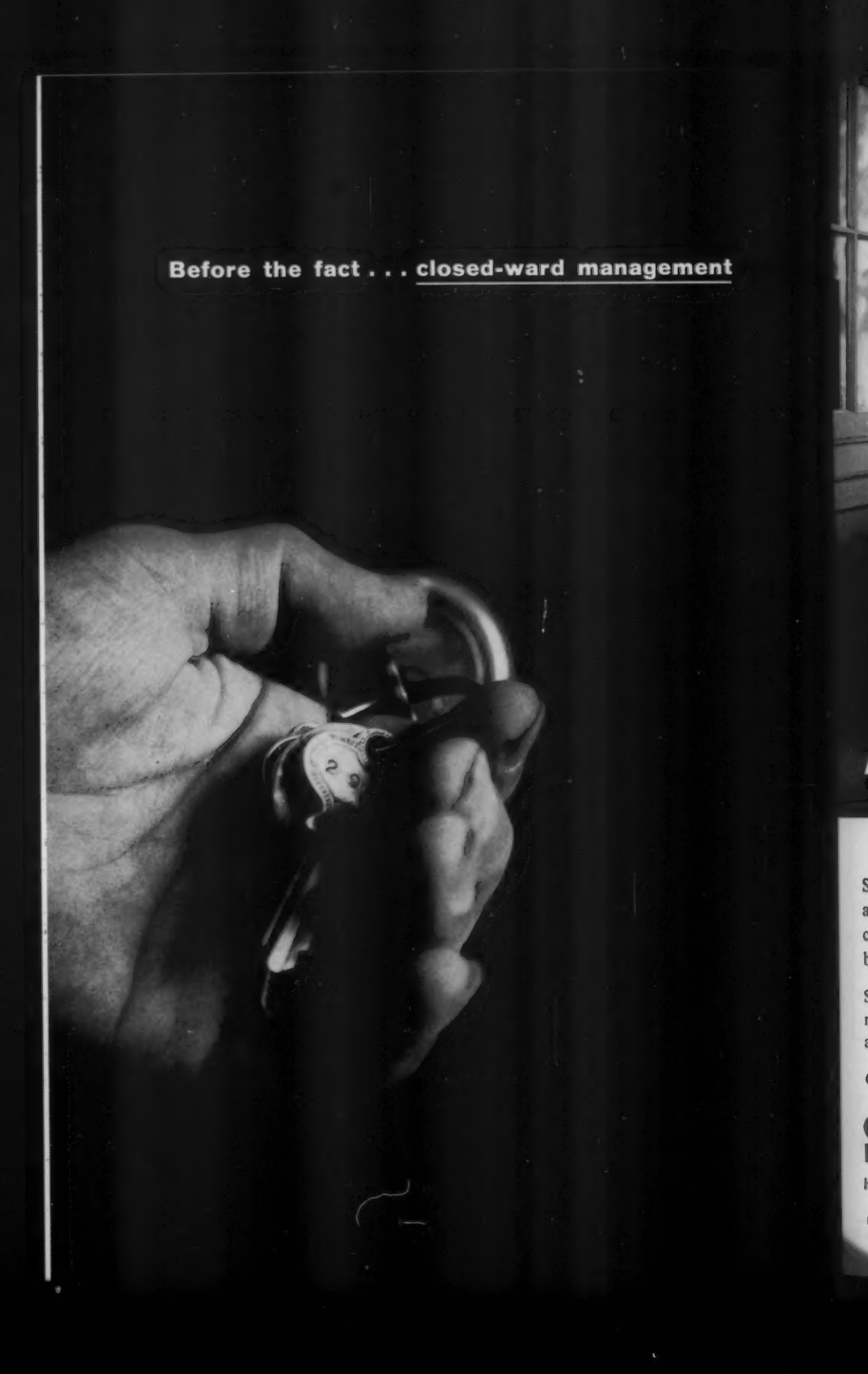
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Neurology Volume 8 • Number 11

Surgical considerations in cerebral arterial insufficiency

W. S. Fields, M.D., E. S. Crawford, M.D., and M. E. DeBakey, M.D.

Occlusion of the carotid artery as a clinical entity has been known since at least 1881, when it was reported by Penzoldt.[1] At the turn of the century, Oppenheim[2] and Gowers[3] discussed carotid occlusion in their respective volumes on diseases of the nervous system. Chiari,[4] in 1905, and Hunt,[5] in 1914, stressed the importance of investigating the carotid arteries in all patients with apoplexy. However, little attention was given to this advice until 1951, when Fisher[6] revived interest in the subject.

A definitive diagnosis of carotid occlusion was not possible without surgical exploration or autopsy until the introduction of cerebral angiography by Moniz.[7] The first report of carotid thrombosis demonstrated by this method was that of Sjöqvist[8] in 1936. The following year, Egas Moniz, Almeida Lima, and de Lacerda[9] reported 4 patients. In 1951, Johnson and Walker[10] reported that routine angiographic examination of 500 patients revealed 6 to have complete carotid occlusion and noted that 101 cases were mentioned in the literature during the previous thirteen years. They suggested, as did Fisher, that carotid occlusion probably is far more frequent than had been suspected previously.

In the present study, more extensive use of angiograms in cases of suspected cerebral arterial insufficiency indicates that a lesion contributing to the syndrome may be located extracranially in approximately 25% of patients. The lesion assumes characteristic locations—namely, the internal carotid artery at its origin from the common carotid artery (Figs. 1 and 2); the vertebral artery in the neck at or near its origin from the subclavian artery (Fig. 3); and the innominate, left common carotid, and left subclavian arteries at their origins from the aortic arch.

PATIENT MATERIAL

This report concerns 71 patients in whom extracranial, occlusive disease of the carotid, vertebral, or innominate vessels was suspected. Extracranial lesions were demonstrated by angiographic examination in 47 patients, and 32 patients with 42 lesions were submitted to operation (Table 1). The lesions found at operation were located in the innominate artery in 5 instances, the left common carotid artery in 4, the subclavian artery in 4, the vertebral artery in 2, and the internal carotid artery in 27. The lesions were bilateral in 10 of the 32 patients, or 31% (Table 2). The lesion was partially occluding in 16 internal carotid, 1 innominate, 4 left common carotid, 2 vertebral, and 3 subclavian arteries and completely occluding in 11 internal carotid and 4 innominate arteries and 1 subclavian artery.

From the Department of Psychiatry and Neurology (Division of Neurology) and the Department of Surgery, Baylor University College of Medicine, Houston.
Read at the tenth annual meeting of the American Academy of Neurology, Philadelphia, April 26, 1958.

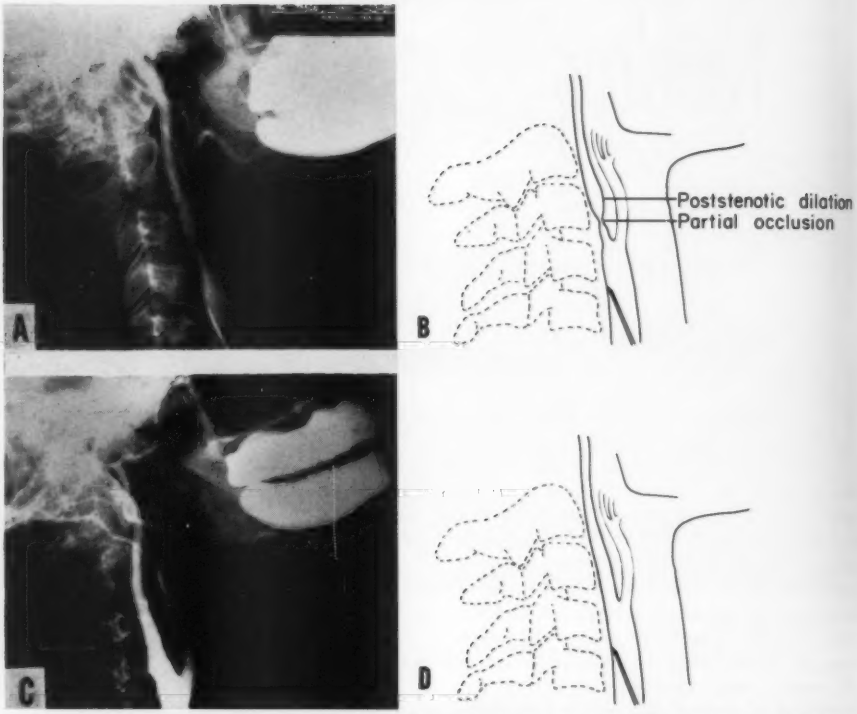

Fig. 1. [A] Carotid arteriogram showing partial occlusion of the internal carotid artery distal to the bifurcation of the common carotid artery. [B] Diagram showing partial occlusion of the internal carotid artery and poststenotic dilation of the normal segment of the internal carotid artery. [C] Carotid arteriogram after thromboendarterectomy showing normal vascular channels. [D] Diagram showing restored arterial lumen of the internal carotid artery.

Only patients with neurologic symptoms suggesting cerebral arterial insufficiency were studied. Although upper extremity symptoms were encountered in the patients with subclavian obstruction associated with involvement of other great vessels originating from the aortic arch, clinical distinction from carotid cases on the basis of neurologic manifestations was not possible. Clinical criteria for selection were episodic or progressive headache, convulsion, motor deficit, aphasia, paresthesia, and visual disturbance. All patients were seen preoperatively by the neurologist to rule out, if possible, other disorders of intracranial origin. This often was impossible without angiographic examination.

PHYSICAL FINDINGS

Aside from the signs of neurologic involvement, which were, at best, inconstant, the physical manifestations of this syndrome were in the blood vessels primarily and consisted of alterations in pulses, bruits, and ocular vessels.

Pulses. Pulsation was absent or diminished in the right arm and right neck if the right innominate artery was occluded and in the left neck if the left common carotid was obstructed. All patients with proximal lesions had such alterations. When the lesion was located in the internal carotid or vertebral arteries, arterial pulsation or its diminution helped

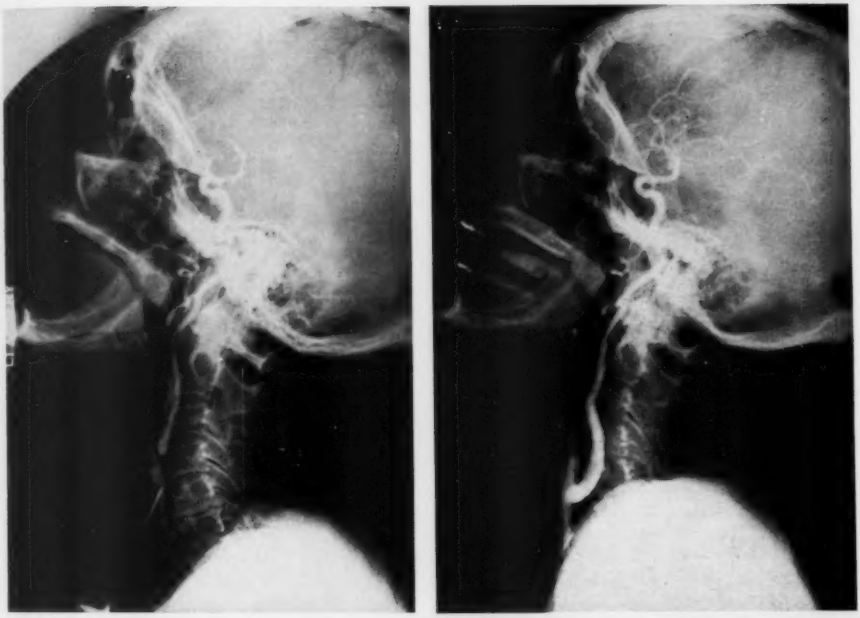

Fig. 2. [A] Arteriogram showing almost complete occlusion of the internal carotid artery at the bifurcation of the common carotid artery. [B] Postoperative arteriogram showing a functioning end-to-side bypass graft restoring normal internal carotid artery circulation.

TABLE 1

RESULTS OF TREATMENT OF 42 OCCLUSIVE LESIONS IN 32 PATIENTS WITH CEREBRAL ARTERIAL INSUFFICIENCY

Location and Type of Occlusion	*Number of Lesions*	*Operable Lesions**		*Successful Results*	
		Number	*Per Cent*	*Number*	*Per Cent*
Internal carotid artery					
Partial	16	16	100	15	94
Complete	11	1	9	1	100
Innominate artery					
Partial	1	1	100	1	100
Complete	4	4	100	4	100
Left common carotid artery					
Partial	4	4	100	4	100
Complete	0	0	0	0	0
Vertebral artery					
Partial	2	1	50	1	50
Complete	0	0	0	0	0
Subclavian artery					
Partial	3	3	100	3	100
Complete	1	1	100	1	100
Total	42	31	74	30	97

*Patent distal segments

Fig. 3. Subclavian-vertebral arteriogram showing partial occlusion of the right vertebral artery at its origin from the subclavian artery.

TABLE 2

MULTIPLE LESIONS IN 32 PATIENTS WITH CEREBRAL ARTERIAL INSUFFICIENCY

Location and Type of Occlusion	*Number of Patients*	*Per Cent of Patients*
Internal carotid artery (bilateral)		
Partial	2	6
Complete	1	3
Partial and complete	1	3
Vertebral artery (bilateral)	2	6
Left common carotid and left subclavian arteries	1	3
Innominate, left carotid, and left subclavian arteries	3	10
Total	10	31

little in diagnosis. When located in the internal carotid artery, the obstructing lesion was associated with a normal external carotid artery in most patients and, frequently, the latter increased in size due to its participation in collateral blood flow. The course of the external carotid artery in the neck and pharynx closely parallels that of the internal carotid artery and may give a false impression of patency.

Alterations in cervical or pharyngeal arterial pulsations could not be detected in any of the 27 patients with proved internal carotid insufficiency or occlusion.

Bruits. In 20 patients, a murmur was audible in the neck over the affected vessel. Systolic bruit in the ipsilateral ear was a prominent complaint in 4 patients.

Ocular changes. Ophthalmodynamometry was not of much assistance in diagnosis, particularly when external carotid collateral circulation was adequate. However, on some occasions, diagnosis was assisted by observation of blanching of the retinal arterioles when the contralateral carotid artery was compressed in the neck.

ANGIOGRAPHIC EXAMINATION

Because of the inconstancy of physical findings, angiographic examination was considered essential for definitive diagnosis and selection of patients for operation.

Bilateral carotid angiograms or cervicothoracic angioaortograms were made in all patients with manifestations of cerebral arterial insufficiency. For carotid angiograms, 8 cc. of 50% Hypaque was injected percutaneously directly into the common carotid artery in locally anesthetized patients. Angioaortograms also were made in locally anesthetized patients by injecting 50 cc. of 70% Urokon through a Robb-Steinberg cannula into an antecubital vein. The aorta and great vessels were visualized by exposing the x-ray film at an interval after injection equivalent to the arm-to-tongue circulation time, which was determined first by injection of 50 cc. of 0.8% Decholin solution.

None of the patients had extreme discomfort, and complications were not significant. Bilateral carotid angiograms were made in most instances during the first half and in all instances during the last half of the study.

PATHOLOGIC FINDINGS

The basis of the occlusion in the 27 patients with internal carotid artery obstruction was a small, discrete, atheromatous plaque located either just distal to the bifurcation or in the common carotid artery at its bifurcation, extending for a short distance into the internal carotid artery (Fig. 4). The remaining segment of the internal carotid artery was essentially normal in 16 patients with incomplete occlusion. Occlusion resulting from superimposed thrombosis was complete in the other 11 patients. In all instances, distal propagation of thrombus did not progress beyond the next main bifurcation. The thrombi in these patients were in various stages of organization, depending upon the duration of occlusion. In 1, occlusion had been complete for only four days and the clot was firm, unorganized, and unattached to the arterial wall. At operation, this clot was easily removed with the atheromatous material and, after a satisfactory backflow of blood was obtained, a distal pulsatile flow of blood was restored. In the remaining patients, the occlusion had been present for eight months to three years and the thrombus was well organized into a fibrous cord in most. In some, however, organization was less complete at the distal end, indicating progression of the thrombotic process over a period of time. Due to organization and extent of the thrombus in these patients, complete removal of the obstruction was impossible by the technics thus far employed. The specimens removed from patients with occlusion of the innominate and left common carotid arteries were not intact and, perhaps, did not reflect the true nature of the disease; however, thrombosis may have occurred distal to a localized atheromatous lesion. Here, as in the internal carotid occlusions, thrombus propagation proceeded only as far as the next distal bifurcation.

Fig. 4. Photomicrogram of specimen removed at operation showing partially occluding atheromas of the internal and external carotid arteries near the carotid bifurcation.

TREATMENT

Treatment was directed toward restoration of a normal pulsatile blood flow to the brain distal to the occlusion. To achieve this objective, 2 types of procedures – thromboendarterectomy and end-to-side bypass graft – were employed (Table 3). Thromboendarterectomy was accomplished by opening the involved artery and removing a localized segment of intima containing the obstructing atheromatous mass. The bypass-graft technic consisted of the insertion of a graft, with 1 end sutured to the uninvolved artery proximal to the lesion and the other end sutured to the uninvolved artery distal to the lesion. For successful application of these technics, the lesion had to be located extracranially and discretely localized, with a reasonably normal patent segment of artery both proximal and distal to the obstruction. Patients were selected for operation on the basis of arteriographic findings. Early in the study, all patients with extracranial lesions were explored. Complete occlusions of the internal carotid and vertebral arteries of more than a few hours' duration usually are not associated with patent distal segments. Consequently, patients with lesions of this type are not suitable for operation. Operation can be

TABLE 3
TYPES OF OPERATION EMPLOYED IN THE TREATMENT OF 42 OCCLUSIVE LESIONS IN 32 PATIENTS WITH CEREBRAL ARTERIAL INSUFFICIENCY

Type of Operation	*Number of Lesions*	*Circulation Restored*	
		Number of Patients	*Per cent of Patients*
Thromboendarterectomy	10	9	90
Graft bypass	21	21	100
Exploration only*	11	0	0
Total	42	30	72

*Patients with advanced disease and paralysis of long duration. Diffuse, organized, superimposed thrombi without patent distal segments

done in patients with partial occlusions of the internal carotid and vertebral arteries and all complete or partial occlusions involving the vessels that originate from the aortic arch (Table 1).

When discrete and well localized to a short segment of artery 1 to 2 cm. in length, the occluding lesion may be removed satisfactorily by thromboendarterectomy. Because of the localized nature of the lesion, the patients in this study with partial occlusions of the internal carotid artery, 1 patient with complete occlusion of the internal carotid artery, and 1 with partial occlusion of the vertebral artery had thromboarterectomy (Figs. 1 and 3). In the remaining patients with internal carotid artery occlusions and all patients with occlusions of the great vessels originating from the aortic arch, the lesion was more extensive. Thus, to simplify the procedure and circumvent the entire diseased segment in these patients, the occlusions were bypassed using a specially designed flexible Dacron tube (Fig. 2). In patients with internal carotid artery occlusions, 1 end of the tube was sutured to the uninvolved common carotid artery proximal and the other end was sutured to the patent segment of internal carotid artery distal to the occlusion. In patients with occlusions of the great vessels originating from the aortic arch, the proximal end of the tube was sutured to the aortic arch proximal to the lesion.[11] The other end of the tube was sutured to the vessel in the neck distal to the occlusion. Straight tubes were used when only 1 vessel was involved, and bi- or trifurcated tubes were employed when more than 1 vessel was affected. In the latter case, the main body of the graft was sutured to the aorta and the limbs of the bi- or trifurcated tubes were then sutured to the vessels beyond the occlusion.

Early in the study, it was felt that the brain needed protection during operation upon partially obstructing lesions and that such protection could be afforded by hypothermia or temporary shunts. Subsequently, it became obvious that these patients could tolerate safely a brief period of complete occlusion. Therefore, shunts were used in only 2 instances – the second patient in the series who had submitted to operation and another patient who had complete internal carotid artery occlusion on the other side and could not tolerate complete occlusion of the partially obstructed artery. The time of complete occlusion during operation was seven to thirty minutes, and all patients recovered without further deficit. Carotid operations were performed with the patient locally anesthetized, both to simplify operation and to detect cerebral changes that may have required use of a shunt.

RESULTS

The results of operation varied both with the location and extent of the lesion (Table 1). For example, a reasonably normal distal circulation was restored in 15 of the 16 patients with partial occlusions of the internal carotid artery. Due to the extensive nature of the lesion and lack of a distal patent segment, circulation was restored in only 1 patient with complete occlusion of the internal carotid artery, which had prevailed for less than three days. Occlusion in the other patients had been

complete for two weeks to several months. Circulation was restored in 1 patient with partial occlusion of the vertebral artery but not in another patient with more extensive occlusion of the vertebral artery. Restoration of circulation was successful in all patients with occlusion of the great vessels originating on the aortic arch. The lesions in these cases were partially obstructing in 8 patients – 1 innominate, 4 left common carotid, and 3 subclavian. In 5 patients, the lesion completely obstructed the vessel – 4 innominate arteries and 1 subclavian artery. Myocardial infarction was fatal in 1 patient, and the neurologic deficit was aggravated in another. The remaining patients in whom circulation was restored had complete relief of symptoms. Preoperative symptoms of 14 patients consisted of intermittent hemiplegia frequently accompanied by aphasia and headache. These symptoms were relieved completely. The longest period of postoperative observation has been five years. Persistent symptoms were relieved in a number of patients, including aphasia in 2, partial blindness in 3, paresis of an extremity in 3, ear noise in 3, and mental obtundity in 3. Follow-up studies during the past five years have indicated that occlusion recurred in only 1 patient treated by thromboendarterectomy. This was the first patient in the series who had operation, and, in light of subsequent experience, early failure was considered due to certain technics that are no longer employed. Hemiplegia occurred in 1 patient after six months, owing to occlusion of the internal carotid artery on the side opposite to operation, but the artery on the side of operation was patent at autopsy. This case is further evidence of the frequent need for bilateral operation.

DISCUSSION

Recent studies of patients with the stroke syndrome reveal that an arterial occlusive lesion may be extracranial in approximately 25% of cases. The practical application of operative technics in these cases represents a distinct advance in the treatment of such patients. Prognosis of patients with cerebral arterial insufficiency treated medically is not good, even when the occlusion is located in the neck. Considering the progressive nature of the arteriosclerotic lesion, longer follow-up studies probably would reveal an even higher incidence of severe disability with medical treatment alone. The excellent results obtained by arterial reconstructive operations in this small group of patients offer considerable hope in the future management of a problem with an otherwise dismal outlook.

To realize the full potential of this new and encouraging form of treatment, a much more aggressive approach must be taken toward the problem of cerebral arterial insufficiency. In our opinion, all patients with cerebrovascular occlusive disease should be suspected of having a potentially curable lesion.

Although extracranial arterial involvement may be suggested by alteration in carotid pulses in some patients, a specific diagnosis usually cannot be made clinically. The clinical manifestations of such lesions are often indistinguishable from those due to occlusion of small cerebral vessels in which surgical treatment is not applicable with present-day technics. Visualization of the cervical and intracranial segments of the carotid arteries on angiograms is essential for accurate diagnosis in all of these patients. This examination, performed percutaneously as an outpatient procedure using 8 cc. of 50% Hypaque solution, is simple and is not accompanied by complications, unreasonable discomfort, and progression of the lesion. Bilateral injections should be done in all patients, even when obstruction is complete on 1 side only. In fact, it is imperative to know whether the lumen is significantly narrowed on the contralateral side in a portion of the vessel where bypass graft might improve circulation.

Operation invariably has been successful in patients with incomplete distal occlusions in or near the carotid bifurcation and with more proximal complete occlusions of the left common carotid or innominate artery. An internal carotid artery that has been completely occluded for a long time rarely is operable, since the atheromatous lesion usually is associated with an extensive superimposed organized thrombus that may extend into the distal portions of the vessel. However, blood flow may, as in the lower extremities, be restored if operation is done early after thrombosis and complete obstruction have appeared. In 1 patient of this series, the small atheromatous lesion and asso-

ciated unorganized thrombus were removed from the internal carotid artery and pulsatile cerebral circulation was restored four days after onset of symptoms. If more patients are to benefit from operation, immediate angiographic examination and early operation are necessary, particularly when neurologic signs persist or recur. Such a course is routine for acute arterial insufficiency of the lower extremities, and the brain, being more susceptible to ischemia, should receive even more conscientious consideration.

SUMMARY

The lesion causing cerebral arterial insufficiency is located outside the skull in approximately 25% of patients with stroke syndromes. Many of these lesions are discrete and localized to a short segment of the internal carotid artery or near the origin of the innominate, left common carotid, or vertebral artery. By employing arterial reconstruction, a more normal cerebral circulation may be restored. Although the diagnosis may be suggested by alterations in carotid pulsations, diagnosis is possible only by angiographic examination. If the maximum potential is to be realized from this treatment, angiographic examination and operation must be performed early and as an emergency when neurologic signs persist.

This therapeutic approach was employed in 32 patients with 27 internal carotid, 5 innominate, 4 left common carotid, 2 vertebral, and 4 subclavian arterial lesions. Of these occlusions, 16 were complete and 26 incomplete. Thromboendarterectomy was done in 9 patients with occlusion of the internal carotid artery or with vertebral artery occlusion. Bypass grafts were employed in the patients with extensive occlusions of the innominate and left common carotid arteries, 7 of the patients with incomplete obstruction of the internal carotid artery, and 14 patients with more proximal obstruction.

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Progressive selective sudomotor denervation

A case with coexisting Adie's syndrome

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In 1955, a 32-year-old man was admitted to hospital because, in hot weather or upon physical exertion, he developed generalized weakness, labored breathing, and fever and was unable to sweat. He was found to have an almost universal anhidrosis. After extensive examinations, his condition was diagnosed as progressive selective sudomotor denervation with preservation of vasomotor and pilomotor functions. This is an unusual clinical condition, and also of interest was the coexistence of Adie's syndrome.

In a comprehensive survey of the literature on anhidrosis, Shelley, Horvath, and Pillsbury[1] point out that this condition may be the result of disturbances in the nervous mechanisms subserving sweating, aplasia or atrophy of the sweat glands themselves, or aplasia, atrophy, or obstruction of sweat ducts. Anhidrosis may be associated with injuries or certain diseases of the skin; occur in some systemic, toxic, or metabolic diseases; or have no defined etiology.

A few cases of acquired generalized anhidrosis have been reported. Fog[2] described a 27-year-old male who had lost his ability to sweat after paratyphoid fever at 21. Biopsy of the axillary skin showed that about one-half of the apocrine glands had degenerated, although the eccrine glands – which are the main source of sweat secretion in man – were not abnormal. Sweating did not occur on exposure to high external temperature or after the injection of 5 mg. of pilocarpine. He assumed the lesion to be in the heat regulating centers of the hypothalamus. However, in review, O'Brien[3] considered this to be a case of tropical anhidrotic asthenia, a sweat retention syndrome due to keratinous plugging of the sweat ducts which became widely recognized in hot climates during World War II.

Engelhardt and Melvin[4] reported the case of a 49-year-old woman who had had generalized anhidrosis for thirteen years. Biopsy of skin from the abdominal area showed generalized atrophy of all sweat glands. O'Brien[3] inferred that this case, too, was one of tropical anhidrotic asthenia. Strauch[5] described a 35-year-old soldier with anhidrosis over the body but hyperhidrosis over the face, palms, and feet which, at the time of presentation, had persisted for eighteen months. Mecholyl bromide produced no sweating over the trunk or extremities. Biopsy revealed a reduction in the number of sweat glands.

Berkman and Horton[6] reported a 36-year-old woman who had been intolerant of heat since the age of 11. Her gait would become weak and slowed, and, at times, she was confined to bed because of weakness. Exposure to external heat provoked slight sweating with a little elevation in temperature. Pilocarpine stimulated slight, generalized perspiration. The patient was considered to have hysteria and was told to sit in the sun. On the third day, after two hours in the sun, she was literally drenched with perspiration. After this, she had no further difficulty, despite days when the temperature was over 110°.

Kuno[7] described an 18-year-old boy who presumably had encephalitic damage to the thermal sweating center when 2 months old. Histologically, he had an adequate number of sweat glands on the general body surface, but they were more or less degenerated. The sweat glands of the palms, soles, axillae, and face were found to be active. He did not sweat on the general body surface when exposed to high

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Fig. 1. The patient's left pupil is myotonic. *(Above)* Before instillation of 2.5% Mecholyl. *(Below)* Constriction after instillation of Mecholyl (Adler-Scheie[8]).

temperatures or on application of pilocarpine by iontophoresis. On his palms and soles and in his axillae, sweating could be produced by mental stress. Sweat over various areas of the face was produced by mental stress or by applying vinegar to the patient's tongue, but not by thermal agents. Apparently, Kuno reports, the centers for sweating on the palms and soles, in the axillae on mental stress, and on the face in response to mental stress or gustatory stimuli were entirely separated from the center for thermal sweating.

CASE REPORT

On July 6, 1955, a 32-year-old accountant was admitted to the Veterans Hospital complaining of excessive fatigability, overheating on exertion, and inability to sweat. He recalled that he perspired freely until 1943 when, as a marine in New Caledonia, he had episodes of fatigue, dull headache, and flushing of the face on exertion. At that time, he did not sweat over the left side of his face and trunk nor over the left upper extremity. By 1950, he had lost the ability to sweat below the waist on the left. During 1951, he observed loss of sweating over the right side of his face, upper extremity, and trunk to the waist. This was followed by anhidrosis of the right lower extremity, so that by 1955 the only area on his trunk from which he sweated was the right flank. Here, perspiration was so pronounced that the adjacent clothing was continuously wet. He found that he tired easily on hot days or after exertion and that his oral temperature after relatively mild exercise was 101.8°. He had also observed that after vigorous chewing, he had a patch of sweat above the left temple. Since the age of 13, he had been aware of a dilated left pupil and found that visual accommodation in this eye was slow.

He had a left mastoidectomy at 8 and an exploratory laparotomy for a suspected nonfunctioning gallbladder at 29. No organs were removed.

Examination: At rest the patient's temperature was 98.6° F., pulse 80 beats per minute, respirations 20 per minute, and blood pressure 110/70. The skin and distribution of hair were normal. A few droplets of sweat were scattered over the forehead. A band of excessive perspiration over the right flank was obvious, and his clothing in this region was wet. Elsewhere there was no apparent sweating. There was a left mastoidectomy and laparotomy scar. The right pupil measured 2 mm., the left, 5 mm. The right pupil reacted briskly to light and in accomodation. The left pupil did not react to these stimuli but constricted excessively after the instillation of 2.5% Mecholyl into the conjunctival sac[8] (Fig. 1). The patellar and Achilles reflexes were absent bilaterally. Meticulous physical and neurologic examinations were otherwise within normal limits.

The patient was readmitted January 13, 1958,

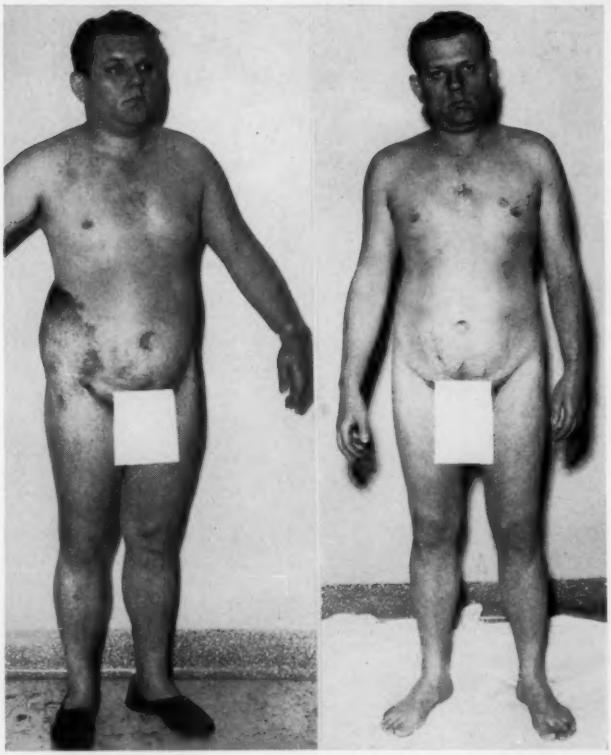

Fig. 2. *(Left)* Spontaneous sweating in July 1955 over right T_{10}, $_{11}$, $_{12}$, and L_1 dermatomes except about hypogastric surgical scar. *(Right)* Progressive anhidrosis by January 1958.

with the same symptoms as before. However, the area over the right flank — which previously had sweated excessively — now was nearly dry. A few drops of perspiration were seen on the patient's forehead. Physical examination was within normal limits. Repeated detailed neurologic examinations revealed no deviations from normal other than those associated with Adie's syndrome. In dermatologic consultation, the skin was considered to be normal by Dr. James Gosman.

Laboratory data: Hemograms and urinalyses were normal. Blood serology was negative. Initial cerebrospinal fluid pressure was 195 mm. of water; dynamics and constituents were normal. Blood urea nitrogen was 16 mg. per cent; sodium, 143 mEq.; potassium, 4.6 mEq.; chloride, 103 mEq.; carbon dioxide, 29 mEq.; total serum protein, 7.8 gm. per cent; albumin, 5.7 gm.; globulin, 2.1 gm.; serum bilirubin, 0.4 mg. per cent; cholesterol, 270 mg. per cent; thymol turbidity, 3 units; cephalin flocculation, negative in twenty-four and forty-eight hours. PSP excretion was 41% in thirty minutes; fasting blood sugar, 97 mg. per cent; glucose tolerance test, normal; and basal metabolic rate, —9.

Two electroencephalograms were normal, as were roentgenograms of the chest, skull, and cervical spine. Gastrointestinal series was normal. The gallbladder could not be visualized.

Sweating tests: For the demonstration of sweating over the general body surface, Quinizarin powder was used; for the detection of sweating in localized areas, the tannic acid paper–ferric chloride method of Silverman and Powell[9] was used.

Spontaneous sweating at room temperature of 82° F. Figure 2, *left,* illustrates the areas of sweating at rest in July 1955. A few spots were present on the forehead, neck, and upper chest, and excessive compensatory sweating is present in the right flank. Figure 2 *(right)* shows the progressive diminution in spontaneous sweating observed in January 1958. There were a few tiny points of sweat from the heel of each hand and the tip of each thumb and little finger. Atropine sulfate, 0.6 mg. injected subcutaneously, abolished all sweating.

Exercise: Riding a stationary bicycle for 2.7

Fig. 3. *(Left)* Distribution of sweating after forty-five minutes exposure to heat in July 1955. *(Right)* Practically universal unresponsiveness to forty-five minutes of heat in January 1958.

miles caused a rise in oral temperature from 98.6 to 100.4°; temperature rose to 102.4° after cessation of exertion. No sweating occurred in anhidrotic areas, but profuse perspiration was present over the right flank.

Thermoregulatory sweating: Figure 3 illustrates the progressive loss of sweating after exposure to external heat between July 1955 and January 1958. During exposure, the patient's oral temperature rose 2° F., his pulse became rapid and weak and his breathing labored, and he became exhausted.

Cholinergic sweating: In July 1955, the subcutaneous injection of 8 mg. of pilocarpine provoked profuse perspiration over the forehead, upper lips, chin, axillae, and right flank as well as over a few areas of the trunk and left thigh (Fig. 4, *left*). In 1958, mecholyl chloride, 20 mg. subcutaneously, induced a generalized erythema and stimulated profuse sweating over the forehead but only slight sweating in the right flank. Progressive hypohidrosis is seen in Figure 4 *(right)*. Intradermal injection of Mecholyl, 1×10^{-4}, into the patient's left forearm and right arm did not cause localized sweating, although in 2 individuals who were serving as controls in this instance, a prompt sweating response appeared.

Emotional sweating: No increase in palmar sweat secretion occurred while the patient was put under emotional stress, nor was there any change in the high galvanic skin resistance noted in the resting state.

Gustatory sweating: Holding spicy and sour materials in the mouth did not evoke any more sweating over the face and forehead of the patient than was ordinarily present. After five minutes' chewing of flavored food, a 2.5 by 7 cm. strip of glistening apocrine sweat appeared in the patient's scalp from the left temple to above the ear and quickly dried upon cessation of chewing.

Pilomotor function: Placing an ice cold, wet towel on the nape of the patient's neck caused immediate generalized piloerection.

Vasomotor function: When the patient reclined, blood pressure was 112/76; when he stood up,

Fig. 4. *(Left)* Sweating provoked by pilocarpine in July 1955. *(Right)* Response to Mecholyl in January 1958. Sweating in the groins in the right picture and to some extent in the left picture is due to contact of skin folds while patient was sitting after injection of cholinergic drugs.

blood pressure was 108/80. Results of a cold-pressor test were as follows:

Base line blood pressure, 104/68
Left hand in cold water at 2:30 P.M.:
2:31.....115/80
2:32.....115/85
2:35.....112/85
Hand removed from cold water:
2:37.....120/80
2:40.....108/75
2:45..... 90/65

These were considered to be normal responses.

The base line blood pressure was 118/60 before a histamine test. No significant change in pressure occurred during the fifteen minutes after intravenous injection of 0.0275 mg. histamine acid phosphate.

Skin biopsy: This was done on two occasions — in December 1957 and in January 1958. Specimens were examined by independent pathologists. The first specimen was taken from an anhidrotic area on the left arm and was reported as normal. On the second occasion, one specimen was taken from an area that had been anhidrotic for several years; another was obtained from the right flank where a small amount of sweating ability was still retained. Both specimens were reported as consisting of normal, stratified squamous epithelium and normal hair follicles, sebaceous glands, and sweat glands. Particular attention was given to the sweat glands: they were normal in number, distribution, and appearance and showed no evidences of degeneration or of obstruction of the ducts (Fig. 5). After careful study of biopsy material taken from an area of minimal residual sweating and from an area of nonsweating, some nerve fibers were found entering sweat glands in both specimens. Figure 6 is from a nonsweating region and shows an anatomically intact fiber.

DISCUSSION

Before attempting to deduce the pathophysiologic nature of the patient's anhidrosis, certain aspects of the phenomenon of sweating should be reviewed. Liberal reference is made to the contributions of Kuno,[7] Rothman,[10] List and Peet,[11,12] and Randall.[13]

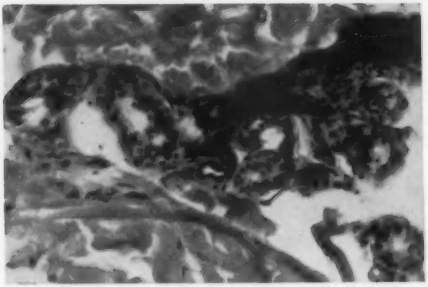

Fig. 5. Skin biopsy from nonsweating area showing normal sweat glands and ducts. H and E stain (Dr. David Rosenbaum).

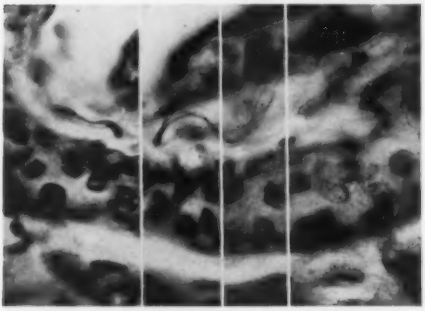

Fig. 6. Composite of a single nerve fiber innervating sweat gland taken at different planes of focus to show its course. Hortega silver-carbonate impregnation (Dr. William DeMyer).

Physiologically, the most important function of sweating is the regulation of body temperature by evaporative heat loss. In addition, sweat helps to maintain the suppleness of the skin and to preserve acute tactile sensibility.

There are various pathways for the neurogenic activation of sweat glands, some being fairly well established and others conjectured.

Thermosensory impulses from receptors in the skin and elevated blood temperatures seem to be the predominant controlling influences which activate centers for thermoregulatory sweating in the anterior portion of the hypothalamus.

In a study of the nuclei of the hypothalamus in 13 patients who died of heat stroke, Morgan and Vonderahe[14] hypothesized that the larger cells of the more anteriorly situated nucleus paraventricularis and cells of the nucleus tuberis lateralis are primarily concerned with the elimination of heat, while the more posteriorly situated nucleus tuberomamillaris and, probably, the smaller cells of the paraventricular nucleus are primarily concerned with the production and conservation of heat.

From these centers, fibers descend principally via the medial and lateral reticulospinal tracts, some being crossed and others uncrossed in the brain stem and cervical cord—passing downward with some intermingling in the anterolateral and lateral columns to synapse in the intermediolateral cell column. Between the first thoracic segment,[15] and evidently as far down as the fourth lumbar,[13] these cells give rise to preganglionic fibers which exit with the anterior roots and enter the sympathetic ganglia by means of the white rami. They may, through the sympathetic trunk, be distributed to 4 to 6 ganglia before synapsing and giving rise to postganglionic fibers. These leave through the gray rami to join the mixed spinal nerves, accompany the sensory fibers to the skin, and innervate sweat glands, blood vessels, and pilomotor muscles in zones roughly corresponding to the somatic segmental distribution, but with more extensive overlapping. There is also evidence for the existence of accessory or intermediate sympathetic ganglia situated most often near the communicating rami, which, because of their inaccessibility, are not removed in a classic sympathectomy. The early recurrence of sweating in denervated areas is considered to be due in part to preservation of these ganglia, rather than to regeneration of sympathetic fibers.[16]

Although the sudomotor, vasomotor, and pilomotor structures are anatomically innervated by sympathetic fibers, there is a high degree of independence of functional response to thermogenic, psychogenic, and drug stimuli. Thus, the eccrine glands respond to cholinergic stimuli, whereas the apocrine glands, blood vessels, and arrectores pilorum respond to adrenergic agents. Despite these differences in action, no conclusive evidence exists that the ganglion cells or their innervating fibers have specifically identifiable morphologic differences.

Characteristically, sweating to emotional stimulation is most pronounced on the palms,

soles, and axillae, although, under some circumstances, it may be generalized. Kuno[7] believes that centers for psychic sweating are located in the cerebral cortex. Netsky and Starr,[17] in a study of patients with cerebral lesions, found that after extirpation of an area of cortex extending anteriorly from the postcentral gyrus to an undetermined distance beyond the precentral gyrus, an increase in sweating, skin temperature, or both occurred on the contralateral side analogous to the area of cortical representation.

Apparently, the cholinergic activation of the eccrine glands occurs at the fiber endings at the neuroglandular junction through the liberation of a chemical mediator, acetylcholine. Such a drug, administered systemically or intradermally, stimulates the normally innervated gland to secrete.

List[11] has indicated that 2 sets of cholinergic fibers exist: [1] postganglionic sympathetic, conveying the majority of cholinergic fibers for the trunk and extremities via the thoracolumbar outflow, and [2] parasympathetic, supplying the head through the fifth, seventh, ninth, and tenth cranial nerves.

After preganglionic sympathectomy, the denervated area does not respond to thermoregulatory sweat stimulation but responds normally to the injection of cholinergic drugs for periods as long as two years.[15] After postganglionic denervation, heat sweating is lost and there may be, for a short time, hypersensitivity of the glands to cholinergic drugs followed by a decrease or loss of responsiveness despite the fact that the gland itself shows little, if any, histologic change.[11,13,18,19] This lack of response by denervated sweat glands – even to intradermally injected cholinergic drugs – is in contrast to Cannon's law that denervated smooth muscles and glands respond excessively to chemical transmitters.[10,18] Because of its complementary innervation by the cranial parasympathetic supply, excessive sweating may occur on the face in response to cholinergic stimulation,[11] a fact demonstrated in the patient described.

In some metabolic disorders, especially diabetes, a medical sympathectomy occurs. Shumacker[20] reported 5 patients, of whom 3 were diabetics, with obliterative arterial disease who had evidence of sympathetic denervation in the legs and feet similar to those seen after lumbar ganglionectomy. He postulated the lesions to be in the sympathetic rami, ganglia, or chain. Odel, Roth, and Keating[21] studied autonomic functions in 40 diabetic patients and found abnormal thermoregulatory sweating patterns in 29. In some, these patterns were patchy in distribution suggesting peripheral sudomotor involvement, but in others, patterns were almost identical to those seen after sympathectomy. Of 30 patients, 13 showed the characteristic postsympathectomy reversal of skin temperature gradient between toes and fingers – the toes being warmer. Of 20 patients, 16 had orthostatic hypotension.

In the patient described here, sweat loss began in the left side of the face and upper quadrant of the body and was followed by loss over the left lower quadrant, then over the right upper and lower quadrants sparing a dermatomal distribution in the right tenth, eleventh, and twelfth thoracic and first lumbar segments. Chronologic sequence is not what one might expect with a lesion of the heat regulating centers in the hypothalamus. It is difficult to conceive of a lesion in this region progressively and selectively implicating neurons in this fashion, particularly in the absence of either neurologic or metabolic syndromes associated with damage in this area. Furthermore, one would expect sweating to occur in response to the systemic administration of cholinergic drugs if the thermoregulatory centers alone were at fault. For the same reason, an appreciable increase in sweating should occur on emotional and gustatory stimulation.

No demonstrable involvement of the brain stem, spinal cord, or peripheral nerves was found, nor was any evidence of diabetes, anemia, renal disease, intoxication, or other systemic affection.

Since piloerection and vasomotor control, which are adrenergic, were normal, the denervation evidently quite specifically involved sudomotor innervation. Flushing of the skin after the injection of Mecholyl indicates that the peripheral vasculature was normally responsive to the muscarinic effects of this drug.

It seems, therefore, that the lesion must be a progressive, selective, sympathetic denervation, and the final dermatomal distribution over

the right flank of compensatory hyperhidrosis followed by hypohidrosis would favor this conclusion. Presumably, if the denervation affected the preganglionic fibers, sweating should have occurred with the systemic and local exhibition of cholinergic drugs. Since it did not, apparently the lesion affected either the sympathetic ganglion cells themselves, their postganglionic fibers, or the neuroglandular junction.

The demonstration of intact nerve fibers entering sweat glands tends to suggest that the disturbance of sweat production lay at the neuroglandular junction and consisted of a defect of acetylcholine–cholinesterase activity. However, the fibers were found only after considerable searching of 60 to 70 serial sections, and, possibly, others were not found because they had degenerated. If this had been the basic site of disturbance, one would expect anhidrosis to develop in patches over different parts of the body. Instead, it occurred in a sequence of dermatomes in a quadrant distribution. This method of development is clinically more in keeping with ganglionic or postganglionic denervation – surgical or medical. The dermatomal quality suggests the site to be in the ganglion cells themselves rather than peripherally in the postganglionic fibers. Apparently, this patient has a progressive, selective dysfunction of unknown cause of the sudomotor ganglion cells.

Assuming that such denervation is responsible for the patient's anhidrosis, one is faced with the problem of trying to determine if there is a relationship between this condition and Adie's syndrome. The lesion here is postulated as being a disturbance of innervation between the pre- and postganglionic fibers in the ciliary ganglion or peripheral to it.[8,22] The etiology for this is unknown. There is no satisfactory explanation for the usually associated absence of muscle stretch reflexes.

It is tempting to ascribe both anhidrosis and Adie's syndrome in this patient to the same pathophysiologic etiology, since both seem to be a disturbance of ganglionic or postganglionic innervation. However, the anhidrosis has been a relatively recently acquired and progressive condition; Adie's syndrome, longstanding and static. Adie's syndrome is not uncommon, yet evidently has not been described in combination with disturbances in sudomotor, pilomotor, or vasomotor function. If these were related disorders, one would expect a more frequent association. Furthermore, it hardly seems logical to combine two disturbances of autonomic function, each of undetermined cause, and ascribe to them a single underlying etiology, itself unknown. It seems more likely that the progressive neurogenic anhidrosis represents a form of medical sympathectomy and that its concurrence with Adie's syndrome is a rare coincidence.

SUMMARY

The physiology of sweating in 1 patient is reviewed. It appears that the pathophysiology represents a progressive dysfunction of those ganglionic cells in the thoracolumbar outflow subserving sweating only – a selective sudomotor sympathectomy.

No cause for this disorder was found in the case presented. The pathogenesis of Adie's syndrome is also unknown. The coexistence of these two conditions in 1 person is probably coincidental.

A 34-year-old man has had Adie's myotonic pupil syndrome for twenty-one years. At 20, he developed a progressive anhidrosis which became almost complete and resulted in fever, tachycardia, tachypnea, and exhaustion on exercising or on exposure to high temperature. Aside from Adie's syndrome, the results of physical, dermatologic, and neurologic examinations were normal. Extensive laboratory studies did not indicate any disorder of metabolic functions. The eccrine sweat glands appeared normal histologically.

There was no appreciable response of the sweat glands to thermoregulatory, cholinergic, emotional, gustatory, or exertional stimuli. Pilomotor and vasomotor functions were retained.

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Nonexistence of the so-called cerebral form of carotid sinus syncope

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THE WORK OF Hering, Heymans, and deCastro, during the twenties, on the anatomy and physiology of the carotid sinus has shown the importance of this structure in certain vasomotor reflexes. It is not the intent of our paper to criticize this work; rather, we wish to point out that when attention was drawn to the carotid sinus, one important observation made in the nineteenth century was forgotten or overlooked: compression of either carotid artery in the neck can result in ischemia of the brain with syncope.

Experimentally, lowering of the intrasinus pressure by compression of the common carotid artery proximal to the sinus results in cardiac acceleration, vasoconstriction, and a rise in arterial pressure with liberation of adrenalin. Pressure of the carotid sinus itself causes slowing of the heart, vasodilation, and fall in blood pressure. In man, no abnormality is noted on compression or palpation of the carotid bifurcation, particularly in young, healthy subjects. In other individuals, one of several responses, or various combinations of these, may be obtained:

1] There may be an irritable carotid sinus, and, on compression or palpation of the carotid sinus, syncope may result due to asystole produced by the cardioinhibitory reflex.

2] A severe drop in blood pressure may occur as a result of the vasodepressor reflex. This is not necessarily associated with syncope.

3] Syncope, unassociated with bradycardia or vasodepression, may occur.

It is this third type of reaction that has been called the cerebral form of carotid sinus irritability. We have found that when syncope occurs upon compression of the carotid artery without bradycardia or a drop in blood pressure, occlusive vascular disease involving the opposite carotid, the anterior cerebral, or the basilar arteries usually exists. We conclude that this type of syncope is due to ischemia of the brain and has been wrongly termed the cerebral form of sinus irritability. A carotid sinus inhibitory reflex may of course also be associated with this ischemic response.

MATERIAL

The findings in this paper were based on a study of [1] the responses of 100 patients with hemiplegia or hemiparesis, exhibiting syncope upon carotid compression; [2] a group of 154 patients tested by carotid compression whose presenting symptoms and signs were other than those resulting from cerebrovascular disease; and [3] a group of 14 patients in whom the blood pressure responses were recorded during carotid compression. This latter group of patients were also seen for complaints other than those resulting from cerebrovascular disease.

RESULTS

Syncopal responses upon carotid compression in 100 patients with cerebrovascular disease. In this group, there were 12 examples of cardioinhibitory response with marked bradycardia or asystole. Angiograms in these patients were normal. In 63 patients, there was angiographic evidence of partial or complete occlusion of the internal carotid artery in the neck, a nonfunctioning proximal portion of the anterior cerebral artery on the opposite side,

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TABLE 1

SYNCOPAL RESPONSES UPON CAROTID COMPRESSION IN 100 PATIENTS WITH CEREBROVASCULAR DISEASE

Type		*Number of patients*
Cardioinhibitory response	Without hemiplegia unilateral asystole — 6 bilateral asystole — 2	8
	With hemiplegia ipsilateral asystole	4
		12*
Ischemic response (occlusive vascular disease)	Complete carotid artery occlusion	11
	Partial carotid artery occlusion	17
	Anterior cerebral artery occlusion	18
	Basilar artery occlusion suspected — 13 confirmed at autopsy — 2	15
	Middle cerebral artery occlusion	2
		63
Combined cardioinhibitory and ischemic responses	Complete carotid artery occlusion contralateral asystole — 3 ipsilateral asystole — 1	4
	Partial carotid artery occlusion ipsilateral asystole — 1 contralateral asystole — 2 bilateral asystole — 1	4
	Anterior cerebral artery occlusion bilateral asystole	4
	Middle cerebral trunk occlusion contralateral asystole	1
		13
Miscellaneous (including vasodepressor response)	Cerebrovascular insufficiency normal angiogram no focal signs — 5 with focal signs — 2	7
	Cerebrovascular insufficiency with vasodepressor response	2
	Intracerebral hematoma	1
	Brain tumor	2
		12

*Except for 1 patient with an aneurysm, all 12 had normal angiograms.

or basilar artery occlusion. It was interesting that, in an additional 13 patients, there was a combination of cardioinhibitory and ischemic responses. In all of these subjects, occlusive cerebrovascular disease was demonstrated by angiography. Evidence of gross distortion of cerebral vessels by brain tumor and intracerebral hematoma was noted in 3; in the remaining 9, no abnormality was detected by angiographic examination. Table 1 summarizes the pertinent information pertaining to this group.

Analysis of 154 patients whose complaints were due to causes other than cerebrovascular disease. These patients were tested by carotid compression on one and then on the other side, with simultaneous recording of the radial pulse. Results are shown in Table 2. There were 52 patients under the age of 40; no syncope or change in the pulsations at the wrist was exhibited in this group. Among 55 patients be-

tween the ages of 41 and 50 were 3 examples of abnormal response; syncope upon right or left carotid compression resulted in 1 patient, another had vertigo from compression of either the right or the left carotid artery, and a third patient had a feeling of numbness involving the left half of the body on right carotid compression and vertigo on left carotid compression. Of 27 patients between the ages of 51 and 60, syncopal responses in 2 were obtained on right or left carotid compression; 5 positive responses were elicited in the 20 patients between 61 and 80 years of age. Severe bradycardia or asystole occurred in only 2 patients in this group.

Response of blood pressure to carotid compression. Blood pressure responses to carotid compression first on one side and then on the other were recorded in 14 patients. The actual values obtained are given in table 3. Syncopal responses occurred in 2 instances, both patients exhibiting cardioinhibitory reflexes with asystole. In the remaining cases, there was a slight rise, no change, or a slight fall in the blood pressure. It was apparent that the patient's blood pressure response was dependent upon various factors: his reaction to the discomfort of the compression; his emotional make-up; his general well-being as regards existing disease, recent activity, or bed rest.

DISCUSSION

When a sensitive cardioinhibitory carotid sinus reflex exists, the mere palpation and stroking of the carotid bifurcation and, in some instances, the carotid artery above or below the bifurcation may result in asystole followed by syncope. Asystole is prompt. Onset of syncope is often within seven seconds, and loss of consciousness is abrupt without aura. There is usually no memory of the experience. Pallor frequently occurs after onset of asystole, but convulsive movements seen in most patients who have occlusive disease with an ischemic effect are not common. Mouth movements, hand groping, hyperventilation, and sweating are unusual. With asystole, blood pressure falls abruptly.

Syncope resulting from carotid compression in the presence of occlusive vascular disease

TABLE 2

RIGHT AND LEFT CAROTID COMPRESSION TESTS IN 154 PATIENTS WITH CONDITIONS OTHER THAN CEREBROVASCULAR DISEASE

Age groups	*Number of patients tested*	*Abnormal response*	
		Number	*Type*
1 to 10	1	None	
11 to 20	4	None	
21 to 30	10	None	
31 to 40	37	None	
41 to 50	55	3	Right, syncope; left, syncope
			Right, vertigo; left, vertigo
			Right, numbness of one-half of body; left, vertigo
51 to 60	27	2	Syncope, then no response
			Right, syncope; left, syncope
61 to 70	16	4	Right, vertigo; left, vertigo
			Right, vertigo; left, vertigo
			Left, tingling right arm
			Right, sensitive carotid sinus (asystole)
71 to 80	4	1	Hypertension, bilateral sensitive sinus (asystole)

TABLE 3
BLOOD PRESSURE RESPONSES TO CAROTID COMPRESSION IN 14 PATIENTS

Patient	Carotid compressed	Blood pressures at fifteen-minute intervals							
No. 1	Right	124/80	110/80	102/80	110/82	118/80	110/80	116/78	124/82
	Left	118/84	116/84	100/76	102/76	106/82	96/68	114/80	118/82
No. 2	Right	154/84	146/90	150/90	154/84	142/80	136/80	136/80	124/80
	Left	130/80	130/86	156/94	168/94	146/92	154/92	134/80	134/80
No. 3	Right	148/78	152/94	166/100	156/106	154/110	158/96	148/94	146/90
	Left	146/78	146/78	148/84	164/94	174/92	156/92	156/82	150/78
No. 4	Right	104/74	104/74	106/80	110/80	112/86	108/84	100/80	100/78
	Left	104/74	106/80	110/84	110/88	106/74	100/72	102/74	102/72
No. 5	Right	140/88	140/100	144/100	140/102	128/80	130/80	132/84	134/82
	Left	132/84	128/84	130/84	130/84	126/80	120/80	126/82	138/88
No. 6	Right	150/90	150/94	150/94	150/90	140/90	130/90	150/90	150/90
	Left	150/94	160/90	160/90	140/88	150/88	150/94	150/94	150/94
No. 7	Right	120/78	112/70	120/70	110/72	110/70	114/76	118/76	114/76
	Left	122/80	110/76	120/78	116/76	116/84	114/72	120/78	122/76
No. 8	Right	170/100	178/112	220/136	228/130	234/138	236/140	204/96	186/102
	Left	168/100	176/108	180/112	178/102	174/110	192/110	190/122	174/102
No. 9	Right	90/58	94/50	84/64	82/60	98/70	94/70	94/70	92/68
	Left	94/70	94/74	96/78	88/66	94/66	90/66	92/68	92/70
No. 10	Right	132/76	130/70	132/76	124/78	130/82	124/80	120/78	126/70
	Left	124/70	120/76	136/76	140/78	138/80	144/92	120/72	124/70
No. 11	Right	140/90	140/86	146/90	140/90	146/86	134/90	134/86	140/84
	Left	140/84	136/80	142/84	138/90	134/80	140/80	152/84	150/90
No. 12	Right	120/76	118/70	124/80	134/86	138/88	130/80	124/82	122/80
	Left	122/78	128/80	136/90	136/86	142/92	128/80	122/78	122/80
No. 13	Right	140/90	110/80	140/100	140/86	138/80	130/80	126/80	120/80
	Left	126/80	134/90	140/90	140/90	140/90	138/84	120/80	124/80
No. 14	Right	106/66	60/?	0?	0?	0?	120/80	140/80	138/80
	Left	140/80	114/80	0?	0?	0?	120/80	130/80	130/80

usually requires ten to twenty seconds of sustained manual occlusion of the carotid artery. Sometimes it may be necessary to compress the artery for thirty to forty seconds to elicit the ischemic response. Collateral circulation may exist to a degree which precludes syncope, but dizziness, vertigo, or malaise may occur. Subjective numbness or weakness of the contralateral half of the body with or without syncope may be experienced. Convulsive movements are commonly seen contralateral to the side of the compression and are greatest in the upper extremity. At times, the jerky convulsive movements may occur without loss of consciousness. Only several twitches may occur, indicating the beginning of the ischemic response. Syncope usually occurs just before the onset of the convulsive movements; these movements may then increase as the patient regains consciousness. There is also slowing of the brain waves just before the onset of syncope. Thus far, we have not observed a generalized convulsion during or after carotid compression. The pattern of movements may be somewhat different in patients with an occlusion of the anterior cerebral artery. Groping movements of one or both arms and grasping or random picking of the bed covers seem common. At this time, a grasp reflex may be demonstrated, possibly attended by mouth movements, including pursing of the lips, grimacing, and lip compressing. In addition, changes in mental status, such as confusion, disorientation, agitation, and an appearance of fear followed by amnesia, are common in all cases so far examined.

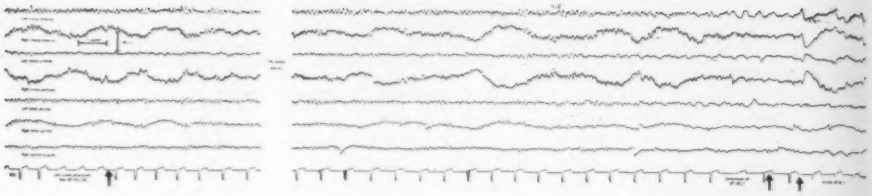

Fig. 1. Vasodepressor response induced by left carotid artery compression. The patient is a 73-year-old white male with episodic syncope, mental confusion, anxiety, and paresthesias in both hands. Hemiparesis was not present. Angiographic examination showed slight stenosis of both internal carotid arteries, and an electrocardiogram indicated minimal cardiac slowing. Blood pressure dropped from 124/100 to 100/0 mm. Hg and returned gradually to 120/100 mm. Hg five minutes after compression was released. Electroencephalographic slowing occurred in the frontotemporal regions, and the patient slumped as if in a faint. There was amnesia for this period, but no convulsive movements occurred.

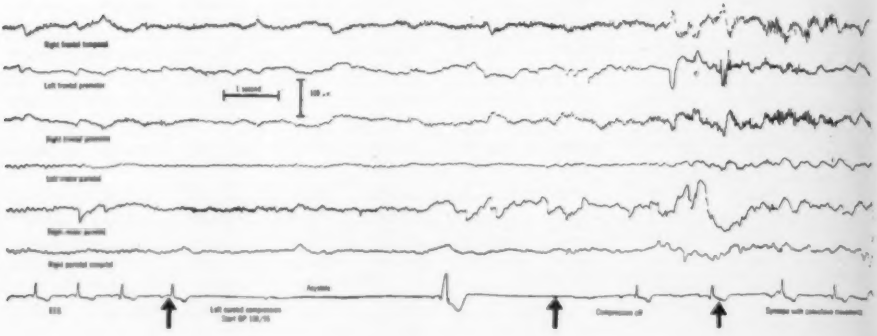

Fig. 2. Cardioinhibitory reflex response. The patient is a 58-year-old white male, with episodic dizziness, paresthesias, and weakness of right hand and left leg. Angiographic examination showed bilateral stenosis of carotid arteries. An electrocardiogram demonstrated cardiac asystole resulting from left carotid artery compression. High voltage delta waves appeared first in the right frontoparietal region and rapidly became diffuse, although a right hemisphere preponderance of slow activity persisted. Syncope occurred, and the spike activity corresponded with left-sided convulsive movements. This patient had bilateral cardioinhibitory reflex responses which were blocked with atropine, and, then, ischemic response with syncope occurred when either carotid was compressed, as both carotid arteries were stenosed.

Among those patients exhibiting an ischemic response, diaphoresis and a fall in blood pressure may be noted. There may be gradually progressive hyperpnea until the rate reaches 30 respirations per minute with an accompanying increase in depth. The electroencephalogram may show slow waves developing as the syncope first becomes evident. Usually, the patients are asked to count as the compression is applied. They are unable to continue with the onset of the ischemic effect, often before syncope begins. Subjective sensations include feelings of dizziness, blurring of vision, and paresthesias. With basilar artery insufficiency, the paresthesias may be bilateral, involving also the face and tongue.

Combined cardioinhibitory and ischemic responses were seen in 13 cases. When these pa-

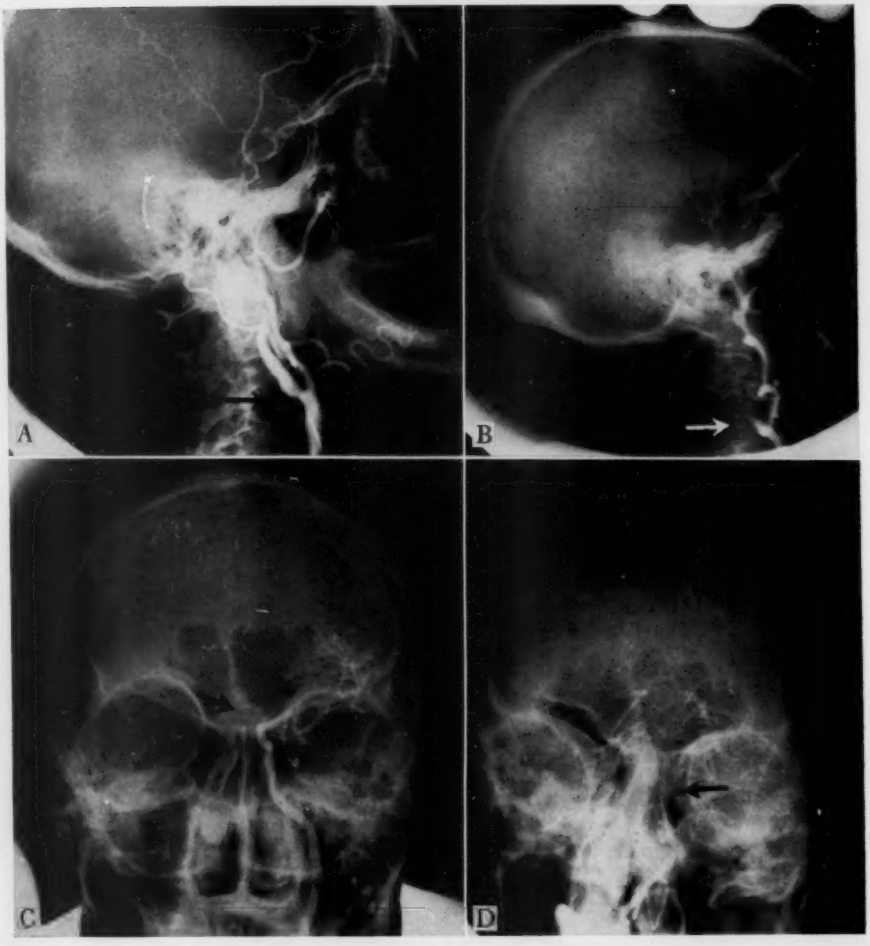

Fig. 3. Angiograms demonstrating the types of occlusive cerebral vascular disease responsible for syncope upon contralateral carotid artery compression. *(A)* carotid stenosis; *(B)* carotid occlusion; *(C)* anterior cerebral artery occlusion; *(D)* basilar artery stenosis.

tients were atropinized, the cardiac asystole was abolished, and continued carotid compression for ten to thirty seconds resulted in syncope. Before atropinization, the syncopal effect occurred much earlier, after five to twelve seconds of compression.

Variations in responses are not uncommon. Some patients appear to build up tolerance for compression as collateral circulation improves – an effect which was demonstrated by Matas many years ago. The first test among patients with the ischemic response often gives the maximal effect. The time allowed for compression; the totality of the compression; the patient's blood pressure at the time of compression; psychologic variations; the position

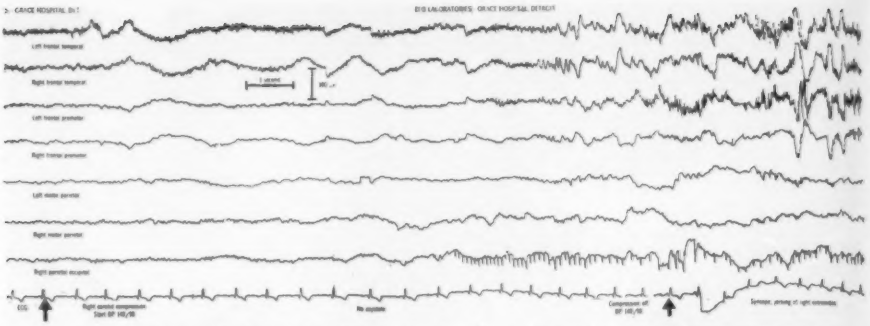

FIG. 4. Occlusive cerebral vascular disease showing syncopal response on right carotid compression. The patient is a 47-year-old white male with right hemiparesis. Angiographic examination showed occlusion of the left carotid artery. An electrocardiogram demonstrated no cardiac slowing effect. Blood pressure remained constant. Slowing of brain waves and spike activity were the result of cerebral ischemia. The first electroencephalographic change was the appearance of high voltage slow waves in the frontotemporal regions which spread to posterior areas. This was followed by spike activity when syncope and right focal seizure occurred. Contralateral occlusive cerebral vascular disease involving the carotid, anterior cerebral, or vertebral basilar vessels is the commonest cause for this ischemic response. The spikes in the right parietal occipital lead are artifacts.

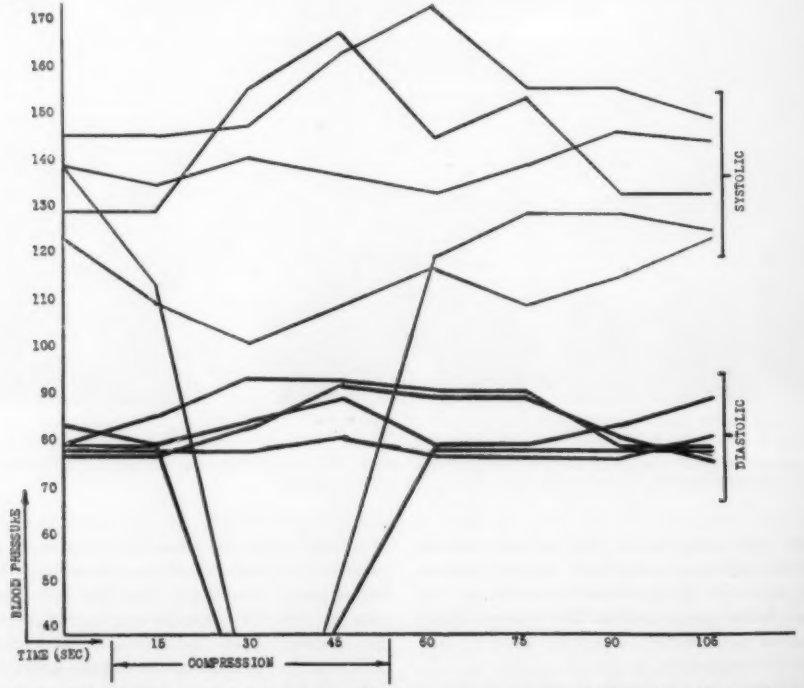

Fig. 5. Graphic illustration of the various blood pressure responses obtained in patients not suspected of having cerebrovascular disease, including a patient having a sensitive carotid sinus.

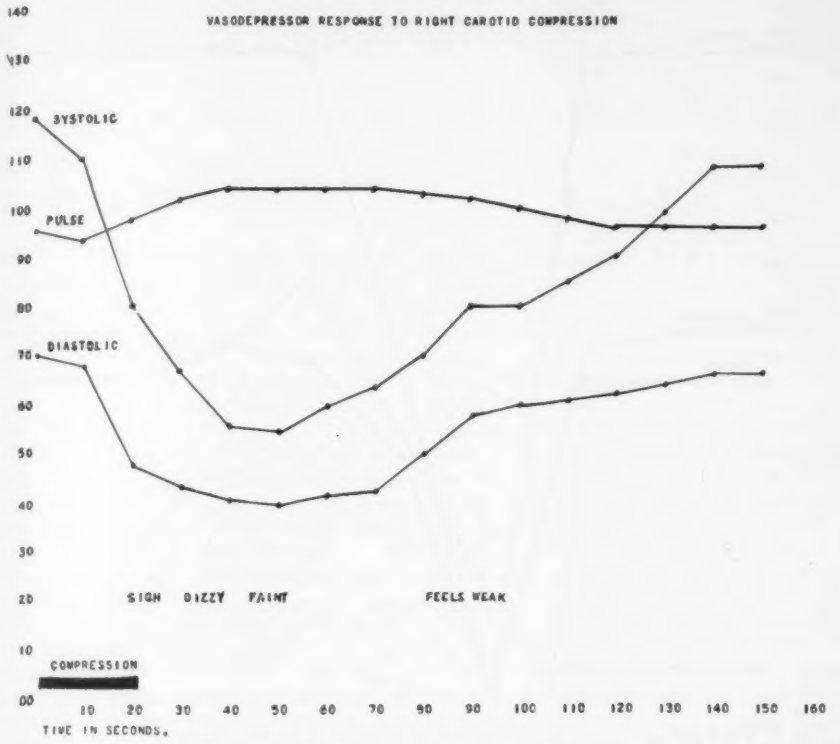

Fig. 6. An example of vasodepressor response to right carotid compression of twenty seconds' duration. Although the drop in systolic and diastolic pressures was quite marked, the patient did not develop syncope. Pulse remained steady, except for a slight rise.

of the patient, whether upright or supine; the time of assuming the upright position for compression; and certain drugs are factors that influence the response, in addition to the state of the cerebral collateral circulation.

The so-called vasodepressor type of response was only occasionally encountered and was usually associated with cardiac slowing. The question arises as to whether the vasodepressor type of response is a carotid sinus effect or a reflex effect with vasodilation in gastrointestinal and muscular vascular bed. Such vasodepressor effects are seen in patients undergoing venipuncture, visiting a hospital, observing blood or bleeding, witnessing an operation, and so forth. In some instances, the compression and palpation of the neck may result in such a vasodepressor effect and may be wrongly ascribed to a sinus irritability. If repeated tests do not produce the same effect, a sinus irritability influence is unlikely.

SUMMARY

An irritable carotid sinus may be associated with a cardioinhibitory effect with syncope due to cardiac asystole. The most common syncopal response induced by carotid compression is the result of partial or complete occlusive cerebrovascular disease involving the contralateral carotid, contralateral anterior cerebral, or the basilar-vertebral systems. It is our impression that many of the responses in this

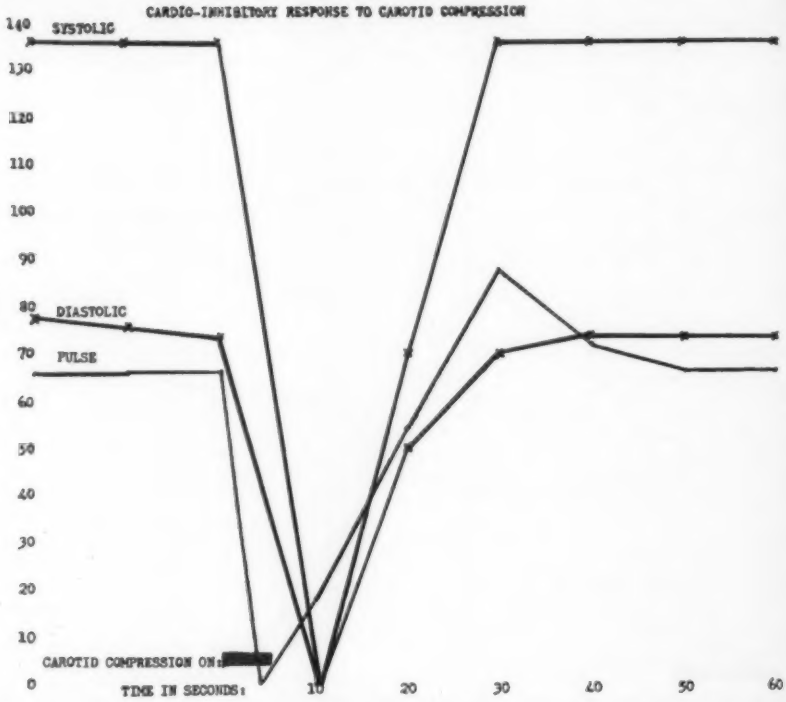

Fig. 7. Blood pressure record of cardioinhibitory response to carotid compression of ten seconds' duration. The blood pressure and radial pulse dropped considerably, and pulsations were inaudible with a mercury sphygmomanometer. When the blood pressure is obtained with a Strain Gauge, the level of the blood pressure is sustained although this level may be less than one-half of the original pressure.

group have been wrongly interpreted as the cerebral reflex type of carotid sinus irritability related to cerebral vasoconstriction resulting from neck compression.[1]

The data presented here indicate that concepts concerning carotid sinus reflexes must be revised in the light of information gained by cerebral angiographic examination of patients whose syncopal responses upon carotid compression have been carefully recorded.[2]

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Further studies on ether convulsions

Fat embolization and its association with neurologic deficits

Guy Owens, M.D.*

CONVULSIONS in previously normal individuals are infrequent but, at times, disastrous complications of ether anesthesia. The etiology has remained obscure. Hyperpyrexia, neurologic deficits, and/or death may accompany ether convulsions. Reproducible phenomena of this type, accurately reflecting the clinical picture, have been consistently produced in animals by combining induced hyperthermia and diethyl ether anesthesia.[1,2] These studies have demonstrated that [1] since motor responses were frequently absent, the electroencephalogram is invaluable in early detection of abnormal cortical activity; [2] among other anesthetic agents similarly studied – divinyl ether, Pentothal, Pentothal plus ether, cyclopropane, chloroform, nitrous oxide, and ethylene – only divinyl ether produced cortical arrhythmias, but, unlike diethyl ether, no central nervous system damage was observed; and [3] the mechanism of the cytotoxic changes in the brain caused by combination of hyperthermia and diethyl ether anesthesia was not clear.

This report deals with studies which develop further some of the specific metabolic changes produced under the clinical and experimental conditions associated with ether convulsions.

METHODS

After a twenty-four-hour fast, 2 groups of 10 healthy dogs were anesthetized with open-drop ether. After endotracheal intubation, ether was administered with 100% oxygen through a closed gas system in which a soda-lime carbon dioxide absorber was incorporated. In group A, rectally measured body temperatures were elevated to 105-107° F. by using a heated rubber blanket. No preanesthetic medication was used. In the same manner, group B dogs were made hyperthermic during anesthesia to temperatures of 110 to 112° F. Prior to anesthetization, 10 mg. per kilogram of sodium heparin† was administered intravenously to group B dogs. In all animals, continuous unipolar and bipolar electroencephalographic tracings were obtained from electrodes located on the scalp overlying bilaterally the region of the motor cortex. Femoral blood pressures and transthoracic electrocardiograms were recorded from each animal. Blood samples were collected from the femoral artery before, and one hour after, anesthetization and, finally, during the occurrence of any electroencephalographic abnormality. If none occurred, a blood sample was obtained at termination of the experiment. Total serum lipid, cholesterol, and phospholipid determinations were made.

All surviving animals were sacrificed two to fourteen days after the procedure. Brain, lung, and kidney tissue from all animals was fixed in 10% formalin for twenty-four hours. Frozen sections of these tissues were then stained with Sudan IV. In those animals demonstrating the most marked neurologic deficits, brain tissue was embedded in paraffin and stained with hematoxylin and eosin, and sections were examined microscopically for pathologic changes.

RESULTS

The 10 animals in group A developed electroencephalographically recorded seizures at temperatures of 102 to 106.5° F. After recovery from anesthesia, each animal, besides loss of balance, had behavioral changes char-

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†Supplied by Upjohn Pharmaceutical Company

GROUP A DOGS

DOG	TOTAL LIPID MG.%	CHOLESTEROL MG.%	PHOSPHOLIPID MG.%	FAT EMBOLI OF BRAIN	NEUROLOGIC DEFICIT
639 CONTROL / DURING SEIZURE	↑ 439 / 327 25%	↓ 152 / 110 21%	↓ 15.5 / 11.5 22%	+	NEG.
649	↓ 586 / 473 19%	↑ 169 / 176 9%	↓ 14.0 / 13.0 7%	NEG.	NEG.
679	↑ 473 / 484	↑ 136 / 154	↑ 11.6 / 12.7	NEG.	NEG.
674	↑ 394 / 416	— 107 / 107	↑ 8.8 / 9.2	NEG.	NEG.
812	↓ 405 / 235 41%	↓ 144 / 133	↓ 10.0 / 7.0 30%	++++	POSITIVE DIED
627	↓ 473 / 452 4.5%	↑ 140 / 184	↓ 12.0 / 10.0 18%	NEG.	NEG.
714	↓ 473 / 450 4.2%	↓ 165 / 154	↓ 14.8 / 10.0 32%	++++	POSITIVE DIED
744	↓ 383 / 338 14%	↓ 70 / 65 7%	↓ 7.5 / 6.3 18%	NEG.	NEG.
797	↑ 486 / 577	↓ 120 / 100	↑ 11.0 / 12.1	NEG.	NEG.
955	↑ 348 / 326	↓ 110 / 103	↓ 5.0 / 3.8 34%	++++	POSITIVE

Table 1. Serum lipid responses in group B dogs subjected to hyperthermia (105 to 107° F.) and ether anesthesia. Percentage values indicate the degree of change from the control determinations. Phospholipid alterations appear to be most significant. Values represent determinations before the experiment and during seizure discharge.

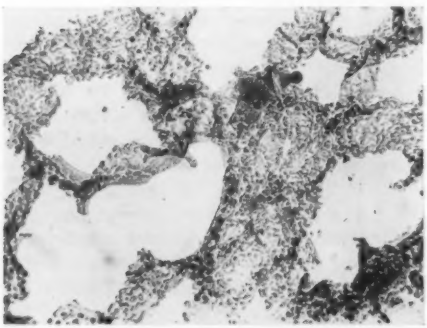

Fig. 1. Frozen section of the lung of dog No. 612(A) stained with Sudan IV. Several globules of fat can be identified in the upper right center portion of this photograph. (High power)

acterized by high-pitched continuous yapping and marked belligerency. Of this group, 7 regained normal ambulation and became docile in the next twenty-four hours. Another animal remained profoundly affected neurologically with disturbed ambulation and balance associated with atonia and tremor. These defects, although improved, were still present at sacrifice two weeks later. The remaining dogs died within twenty-four hours after the experiment.

During the experiments, none of the animals developed hypotension, cardiac irregularities, or respiratory disturbances. Serum lipid chemistry determinations, as illustrated in Table 1, provide little significant information except for a decrease of phospholipids of 30% or more in those animals demonstrating severe neurologic defects and, as will be noted later, significant amounts of cerebral fat emboli. These animals, as well as the others in group A, demonstrated no definite pattern of total serum lipid and cholesterol values. The control total lipid figures ranged from 158 to 812 mg. per cent in the 10 animals. Again no relationship seemed to exist between the degree of abnormal electroencephalographic activity or neurologic disturbances and the level of circulating fat.

The 8 animals surviving the experiments were sacrificed twenty-four hours to two weeks later. Sections stained with Sudan IV demonstrated pulmonary fat emboli in all 10 animals. The greatest amounts were found in 2 dogs that died as a result of the experiment (Fig. 1). Very few pulmonary fat emboli were found in 2 animals sacrificed after two weeks, and these findings may reflect normal variations. None of the animals were found to have stained fat within the glomerular vessels of the kidney. Varying degrees of kidney tubule fat, both intracellular and within the lumen of the tubules, were observed. This probably represented a normal pattern of lipid distribution within the kidney.[3]

Fat was observed rarely in the 7 animals with temporary central nervous system defects in the cerebral tissues. When found, fat was usually located within cells of the capillary wall. These probably were clasmatocytes, although their endothelial origin could not be excluded. The 2 animals that died as a result of the experiment and the 1 that developed profound and persistent neurologic damage had large quantities of embolic fat located within the lumen of cerebral and cerebellar capillaries (Fig. 2). The latter animal, sacrificed after two weeks, also had large amounts of fat located within cells lining the capillaries. The frequency of intracellular capillary fat in this dog suggests that plugged vessels may have been opened by phagocytic action of these cells.

Previous work[4] has identified the pathologic changes found on permanent sectioning of brains from animals in which neurologic defects were induced by combining ether anesthesia and hyperthermia. In the 1 animal in group A that sustained severe and prolonged neurologic damage, the absence of cerebellar Purkinje cells was again remarkable (Fig. 3). No evidence of phagocytosis, gliosis, or damage to other regions of the brain was found; nor was evidence of localized parenchymal necrosis about the cerebral and cerebellar cortical capillaries.

Of 10 animals in group B subjected to hyperthermia (110 to 112° F.) and ether anesthesia after heparinization, 9 failed to develop electroencephalographic seizure patterns – although in 2 dogs, high-spike, slow-wave responses appeared toward the end of the procedure. Postexperimental recovery was prompt and unattended by behavioral or motor changes customarily seen in group A dogs during this period. Of these 9 animals, none developed neurologic disturbances. Burns of the thorax and abdomen, however, occurred commonly – blanket temperatures were around 150° during the two to three hours of the experiment.

After two hours of exposure to heat and ether, the tenth animal developed an electroencephalographic seizure at a temperature of 111° F. During the immediate recovery period, and later, this animal demonstrated central nervous system changes similar to those observed in group A dogs. At sacrifice on the third postexperimental day, loss of balance persisted. All group B dogs survived the experiment and the immediate postexperimental period. No attempt was made to reverse the heparin effect.

Serum lipid determinations were not remarkable, except for a phospholipid decrease of 47% in the animal that convulsed during the experiment and later demonstrated neurologic disorders (Table 2).

These animals were sacrificed twenty-four hours to six days after the experiments. No pulmonary or kidney fat emboli were found. Occasional fat located in cells making up the wall of cerebral and cerebellar capillaries was found in 3 animals, which may represent normal lipid distribution within the vessel walls. Of these 3 animals, the 1 affected neurologically also had cerebral and cerebellar capillary fat embolism. These 3 animals, interestingly enough, were the same dogs that developed abnormal electroencephalographic patterns. Permanent sections of the brain from the animal that demonstrated mild neurologic alterations revealed some decrease in the cerebellar Purkinje cell numbers, mild generalized

GROUP B DOGS (HEPARIN 10 MG./KG. TEMP. 110° – 112°)

DOG	TOTAL LIPID MG%	CHOLESTEROL MG%	PHOSPHOLIPID MG%	FAT EMBOLI OF BRAIN	NEUROLOGIC DEFECIT
745 CONTROL DURING SEIZURE	↑ 788 812	↑ 252 285	↑ 19.8 22.0	NEG.	NEG.
765	↓ 394 372	↓ 110 100	↓ 7.9 6.0 20%	+	NEG.
773	↑ 158 180	↑ 52 56	↑ 3.7 4.5	NEG.	NEG.
776	⇒ 440	↑ 125 130	↑ 11.8 12.9	NEG.	NEG.
734	↓ 754 597	↓ 225 190	↓ 18.7 16.1 17%	NEG.	NEG.
807	—	—	—	NEG.	NEG.
737	↓ 281 259	↑ 72 82	↑ 5.0 6.5	NEG.	NEG.
744	↑ 406 440	↓ 146 138	↑ 12.1 13.7	NEG.	NEG.
909	↓ 417 293	↓ 152 119	↓ 6.4 3.4 47%	+++	POSITIVE
980	↓ 383 293	↓ 162 130	↓ 5.2 4.1 21%	+	NEG.

Table 2. Serum lipid responses in group B dogs subjected to hyperthermia (110 to 112° F.) and ether anesthesia after heparinization. Heparin afforded considerable protection to the central nervous system in the presence of very high temperatures as indicated by the single animal that developed neurologic disturbances. Values represent determination before and at the terminations of the experiment.

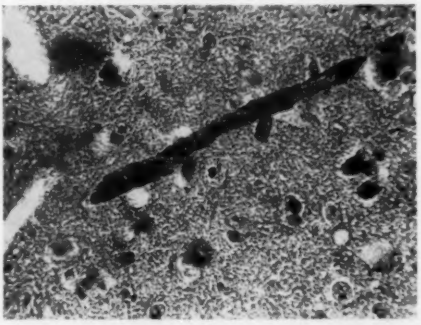

Fig. 2. Frozen section of brain (cerebral cortex) of dog No. 714(A). An embolus of fat occupies the lumen of a large capillary and a portion of one of its branches. (High power)

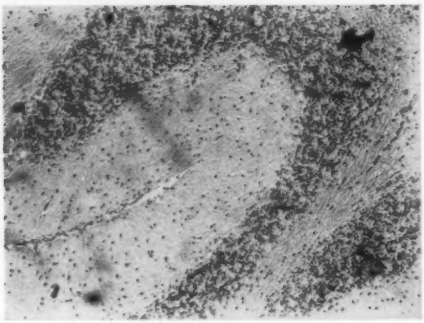

Fig. 3. Hematoxylin and eosin stained permanent section of cerebellum from dog No. 955(A). Note absence of Purkinje cells. (High power)

cerebral neuronal damage characterized by nuclear pyknosis, and occasional cytoplasmic swelling associated with clumping of the Nissl substance. There was no phagocytosis.

DISCUSSION

The discovery of embolic fat associated with ether anesthesia is not original with this work. In 1927, Lehman and Moore,[5] in a study of colloid properties of blood and traumatic fat emboli, demonstrated that ether, added in vitro to prepared fat emulsions or to human plasma, precipitated the homogenized fat in all circumstances. Animals killed by inhaled or intravenously administered ether were also found to have varying amounts of coalesced fat in the lungs. Lehman and Moore also observed that recent feedings made the animals more susceptible to the development of fat emboli when exposed to ether.

Our study has broadened these observations:

1] The animals in this study received ether only in amounts required to maintain a satisfactory level of anesthesia. The same quantities of ether at normal body temperatures in dogs failed to promote development of fat emboli.[6] The addition of hyperthermia must therefore have contributed to fat embolization in some fashion.

2] The serum phospholipid response in group A dogs and 1 animal in group B is of interest. O'Brien,[7] writing on fat ingestion and associated increase in blood coagulability, indicates that the phospholipid fraction is an agent present in platelets as well as in the serum that may activate the clotting of blood. It might be assumed then that there was a close association between the considerable fall in phospholipid levels and the widespread cerebral, cerebellar, and pulmonary fat emboli observed microscopically in these same animals.

3] In group B dogs to which heparin was administered and extremely high temperatures were used, central nervous system protection was afforded in the majority of instances, and the serum phospholipid values, except in one instance, remained unaltered.

The absence of capillary or parenchymal necrosis about embolic fat material is worth some speculative comments. Possibly, capillary endothelial reaction to plugs of fat is absent – allowing the capillary pressure to force the embolus through into the venous circulation. The emboli demonstrated microscopically may then have just reached that position when circulatory standstill occurred. Temporary or permanent tissue damage may result only when the coalesced fat particles are numerous enough in the circulating blood to produce a generalized, sustained low-grade ischemia. The absence of local tissue damage could account for the dramatic complete recovery of patients with severe fat embolism after days, and even weeks, of coma. Or, possibly, despite occlusion of the vessels, prompt removal of the fat by the capillary cells observed in this study may continually reopen circulatory pathways.

The value of heparin in these experiments, regardless of whether it promotes clearing of fat emboli or not, would seem to be the agent's action in preventing fibrin collections – as sludging of blood increases during hyperthermia.[8–10] Anoxia produced by sludging of blood added to intermittently fat-occluded capillaries might readily produce the central nervous system pathology encountered in experimental and clinical ether convulsions. Since traumatic fat embolism characteristically is complicated by a temperature elevation, possibly heparin, under these circumstances, works in a similar fashion. This would lead one to wonder whether heparin, in the presence of febrile convulsions, might not afford beneficial effects.

Several questions may have been answered by this study. Many still remain: Why do barbiturates afford protection to the central nervous system when administered before and during ether convulsions? Is anoxia the chief cause of convulsions and central nervous system damage in view of this fact? What role does fat metabloism play in the ether convulsion phenomena?

SUMMARY

Electroencephalographically recorded seizures developed at temperatures ranging from 102 to 106.5° F. in 10 dogs subjected to hyperthermia (105 to 107° F.) and ether anesthesia. Microscopic examination of brain and lung tissue from these animals demonstrated a high incidence of fat embolization. A good correlation existed between the development of neurologic deficits, microscopic fat emboli, and a decrease in serum phospholipid levels. A second group of 10 dogs heparinized before ether anesthesia were made hyperthermic to 110 to 112° F. Of 3 dogs, 2 developed abnormal wave patterns and 1 had electroencephalographic evidence of a frank seizure. Only the latter animal developed neurologic deficits and evidence of embolic fat. Neurologic disorders after ether convulsions may be explained by blood sludging from temperature elevation and development of fat emboli. Either or both of these factors apparently respond in some fashion to heparinization — resulting in a decrease in neurologic disturbances.

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Histopathology of the mammillary bodies in alcoholic psychosis

Leopold Liss, M.D.

LESIONS OF ALCOHOLIC PSYCHOSES have, in most histopathologic studies, been found most frequently in the mammillary bodies, corpus callosum, and cerebellum, less frequently in various cortical areas and the white substance. Pathologic changes have been considered nonspecific, consisting of a loss of neurons, degeneration of ganglion cell bodies and axis cylinders, astroglial proliferation, microglial activity, and proliferation and degenerative changes of the vascular wall.

In the present investigation, new histologic technics have made it possible to analyze carefully the degenerative changes in neurons and glial elements.

MATERIAL AND METHODS

Brains were removed during routine postmortem examinations, cut in thin slices, and fixed in brom formalin (Cajal's solution). Routine H and E sections from various areas were examined, and numerous blocks from different regions were impregnated with variants of Hortega's silver carbonate technic.[1,2]

Case 1. A 64-year-old male was described as a schizoid, who had drunk approximately 1 pt. of whiskey a day since the age of 21. Symptoms prior to commitment were bizarre, grandiose behavior, later confusion, hallucinations at times, and threats of suicide. At the age of 58 he was committed to a state hospital with a diagnosis of Korsakoff's psychosis. During six years in the hospital, he suffered from chronic gastritis with hemorrhages, anemia, and chronic heart disease. Four years before death, a tuberculous lesion developed in the right upper lobe. A cerebrovascular accident occurred two years, and another four days, before death.

Gross pathologic findings: Brain weight was 1,450 gm. Atheromatous plaques were found on the vessels, also a large area of encephalomalacia due to occlusion of branches of the left middle cerebral artery, and an old softening in the right parietal lobe. Mammillary bodies were atrophic.

Microscopic examination: The part of the brain not affected by the softening was examined histologically with silver. With the exception of encephalomalacia in the left frontotemporoparietal area, no significant pathologic changes were found in the hemispheres or cerebellum.

The corpus callosum showed degeneration of nerve fibers with destruction of the myelin sheaths and fragmentation of the axis cylinders (Figs. 1 and 2).

In the mammillary bodies (Fig. 3), there was a dense proliferation of astroglia, most pronounced in the central area. Under higher magnification, this area resembled a dense scar, with no neurons (Fig. 4). Connective tissue technic showed marked vascular proliferation limited to the central area (Fig. 5).

By Hortega's double impregnation technic, designed to visualize the ganglion cells and the neurites selectively, the periphery was impregnated more darkly than the central portion. This was because of an almost complete absence of neuronal elements in the central portion, and the presence of islands of neurons in the periphery (Fig. 6). Normal ganglion cells were not found; those in the periphery were markedly degenerated and arranged in groups (Fig. 7). In the deeply impregnated cell bodies, different stages of disintegration could be observed (Fig. 8). The neurites of the ganglion cells were swollen and fragmented (Fig. 9) and surrounded by oligodendroglia and astroglial remnants broken into annular formations (Fig. 10).

The degenerated neurons with their fragmented axis cylinders gave rise to peculiar formations, consisting of degenerated cell bodies surrounded by concentrically arranged fragments of neurites (Figs. 11 and 12).

Case 2. A 71-year-old male had been admitted to a state hospital at the age of 56 with a diagnosis of chronic alcoholism since prohibition and Korsakoff's psychosis. Mental symptoms had appeared one year before admission, consisting of forgetfulness and untidy personal appearance; upon development of a persecution complex, he was committed.

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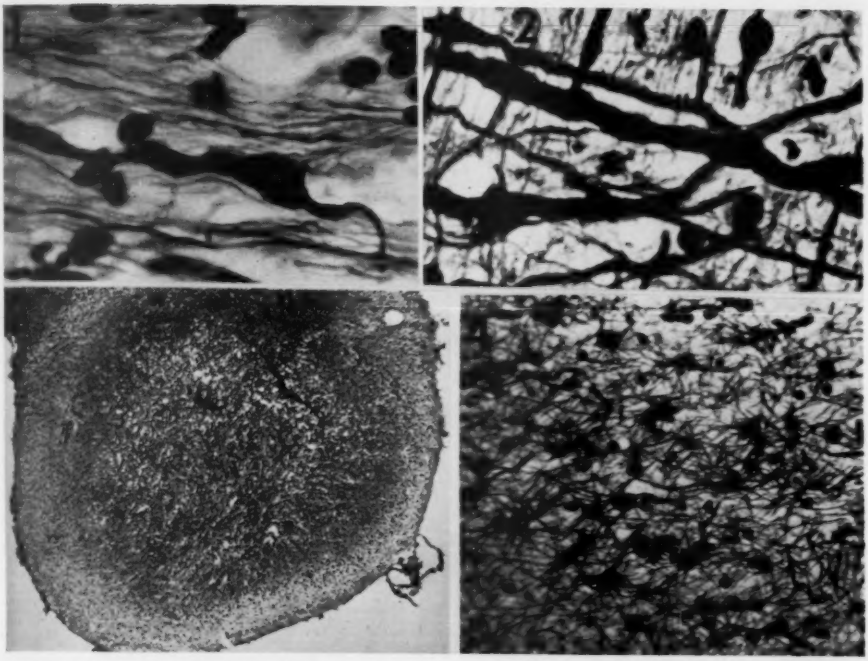

FIGS. 1 and 2. *Case 1.* Corpus callosum, showing severely degenerated nerve fibers with destruction of myelin and fragmentation of axis cylinders (× 1,000)

FIG. 3. *Case 1.* Mammillary body; astroglial impregnation shows dense gliosis in the central area. (× 25)

FIG. 4. *Case 1.* Glial scar formation from Fig. 3 under higher magnification (× 160)

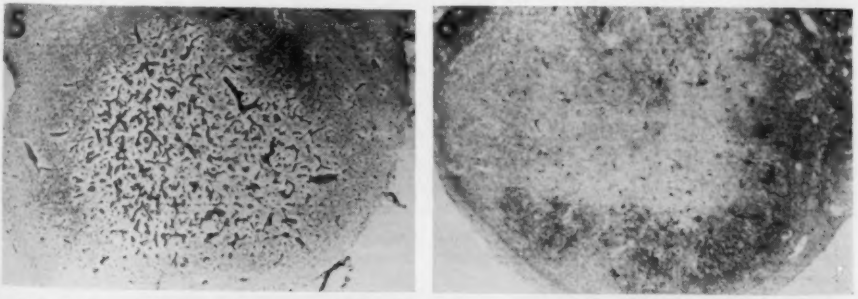

FIG. 5. *Case 1.* Connective tissue. Proliferation of vessels and connective tissue is limited to the central area. (× 25)

FIG. 6. *Case 1.* Neuronal elements, showing almost complete absence of ganglion cells from the central portion, and scattered islands of remaining neurons in the periphery (× 25)

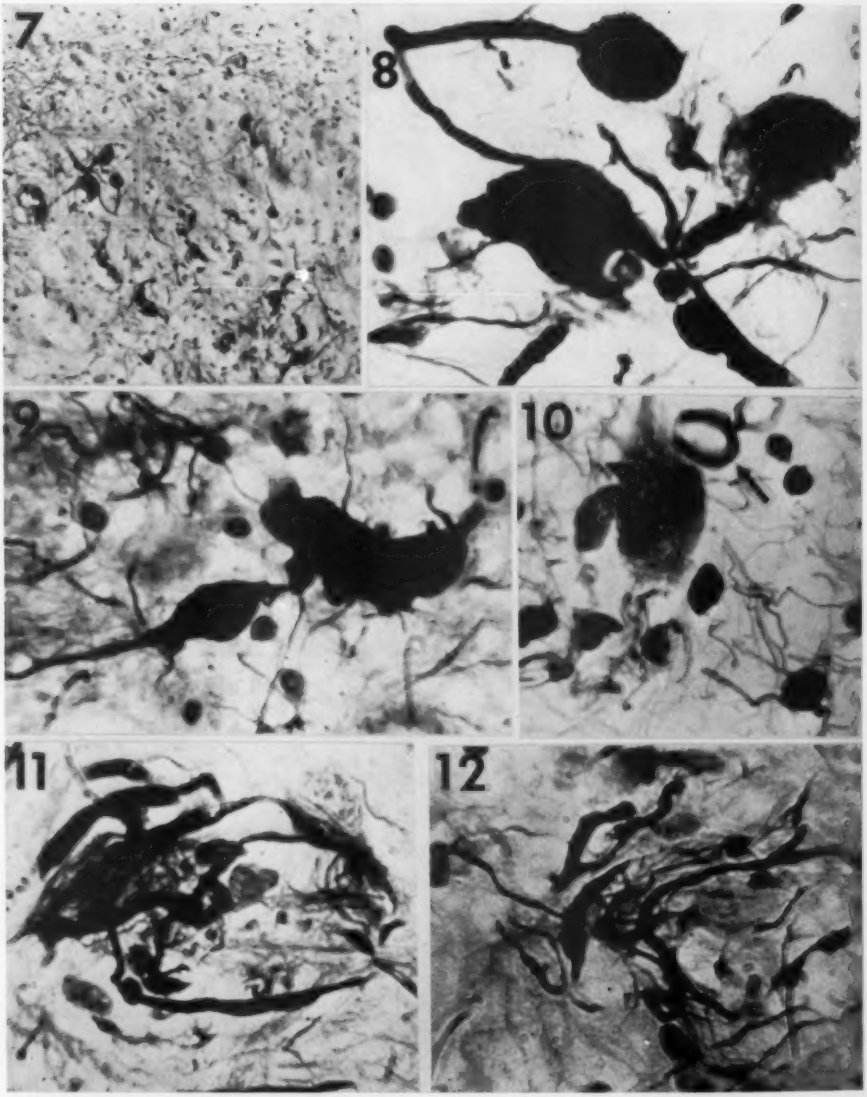

FIG. 7. *Case 1.* Abnormal ganglion cells, some forming clusters (× 160)
FIG. 8. *Case 1.* Part of the field from Figure 7. Neurons have deeply impregnated cell bodies and neurites. (× 1,000)
FIG. 9. *Case 1.* Disintegrated ganglion cell body with grotesquely swollen neurites (× 1,000)
FIG. 10. *Case 1.* Severely damaged ganglion cells surrounded by oligodendroglia. Fragmented astroglia processes form rings (see arrow). (× 1,000)
FIGS. 11 and 12. Peculiar end product of neuronal degeneration. Disintegrated cell bodies are surrounded by concentrically arranged fragmented processes. (× 1,000)

Gross pathologic findings: The body was icteric. The brain weight was 1,300 gm., the mammillary bodies were atrophic, and the large vessels were moderately theromatous. The liver was small, nodular, and hard; cirrhosis was confirmed by microscopic examination. Nothing abnormal was found in other organs.

Histologic examination: Different areas of the brain and cerebellum disclosed only mild senile regressive changes. In the mammillary bodies, numerous neurons were degenerated, only an occasional normal parenchymal cell being present. The degenerated neurons showed enlargement of the cell body, often with vacuolization of the protoplasm (Fig. 13). Frequently, the entire body of the cell disintegrated in a characteristic manner by forming several bulblike swellings; also the neurites of these cells were swollen and fragmented (Fig. 14).

Cells in more advanced stages of degeneration were homogeneously black, impregnated structures barely resembling a neuron (Fig. 15). Some of the degenerated neurons tended to assume skeinlike formations and concentric structures which were not as distinct as in Case 1 (Fig. 16). In the degenerated mammillary bodies were found destroyed neurons with a homogeneously black impregnated cell body and neurite (Fig. 17). In the vicinity of the destroyed ganglion cells, evidence of degenerated astroglial fibers in ring formations could be seen (Fig. 18).

The perivascular structures were also affected by the pathologic process. Around normal or only slightly damaged neurons, the perivascular structures appeared normal. Astrocytes and perivascular glial cells with their fine processes could be easily distinguished surrounding the vessel (Fig. 19). In the areas of severe degenerative changes, the glial perivascular structures were also severely damaged, and the remaining glial fibers were markedly thickened and proliferated (Fig. 20).

Case 3. A 71-year-old male, a chronic alcoholic for 40 years, displayed symptoms of delirium tremens and was committed to a state hospital four years before death.

Gross pathologic findings: The brain weight was 1,370 gm.

Histologic examination: Numerous senile plaques were seen in the cortex of the hemispheres. The neuronal elements of the mammillary bodies were destroyed, 3 types of ganglion cell degeneration being distinguishable: [1] Some of the neurons had a homogeneously black cell body with a thickened, sometimes fragmented neurite (Fig. 21). [2] Others showed changes similar to the fibrillary degeneration of Alzheimer (Fig. 22). [3] The last type of fibrillary degeneration, quite different from senile and presenile degeneration, contained a fibrillary conglomerate of intertwined argyrophilic fibers; some of these processes may have represented the dendrites, the others astroglial processes (Figs. 23 and 24).

Case 4. This 67-year-old woman had a two-year history of alcoholism before commitment to the state institution where she was hospitalized for fourteen years. A stroke six years before death left her with left hemiparesis. She was treated for syphilis because of a positive Kahn test. Cause of death was bronchopneumonia. Final clinical diagnosis was chronic brain syndrome associated with cerebral arteriosclerosis and alcoholic psychosis.

Gross pathologic findings: The brain weight was 1,100 gm. Brain atrophy with old softening involved the right motor area. The mammillary bodies were very small with slight umbilication in the center. Rheumatic endocarditis, liver cirrhosis, and carnification of the lower lobes of both lungs were also found.

Microscopic examination: The mammillary bodies showed a loss of neurons with marked gliosis and degenerative changes in the central portion. Neuronal changes differed from those of previously described cases in that the neurons were distinctly enlarged and spherical, the neurites distinctly swollen and fragmented (Fig. 25). This type of pathologic changes was not found in neurons from other examined areas of the brain.

COMMENT

In Case 1 (Korsakoff's psychosis), the mammillary bodies were atrophic. Vascular proliferation and loss of neurons were marked. Some types of neuronal degeneration were specific in character (skein formations); others were nonspecific homogenization and disintegration of the cell bodies and neurites. The skein formations do not resemble any known type of pathologic changes. Changes in the corpus callosum may be attributed either to the primary alcoholic degeneration or, likely, to arteriosclerotic encephalomalacia. The annular formations of fragmented astroglial processes were nonspecific.[3]

In Case 2 (Korsakoff's psychosis), histopathologic changes were limited to the mammillary bodies. Though similar to the findings in Case 1, they were less pronounced. Concentric degenerative formations were also found, but less prominently than in Case 1. The patchy pattern of degenerative changes – relatively well-preserved areas alternating with severely degenerated ones – was very pronounced. The degenerated perivascular glia, a nonspecific result of severe degneration, can be observed in various areas of the central nervous system.[4]

Cases 3 and 4, although showing distinct gross and microscopic pathologic changes in the mammillary bodies, did not present a clear clinical picture. Both had a history of alcohol

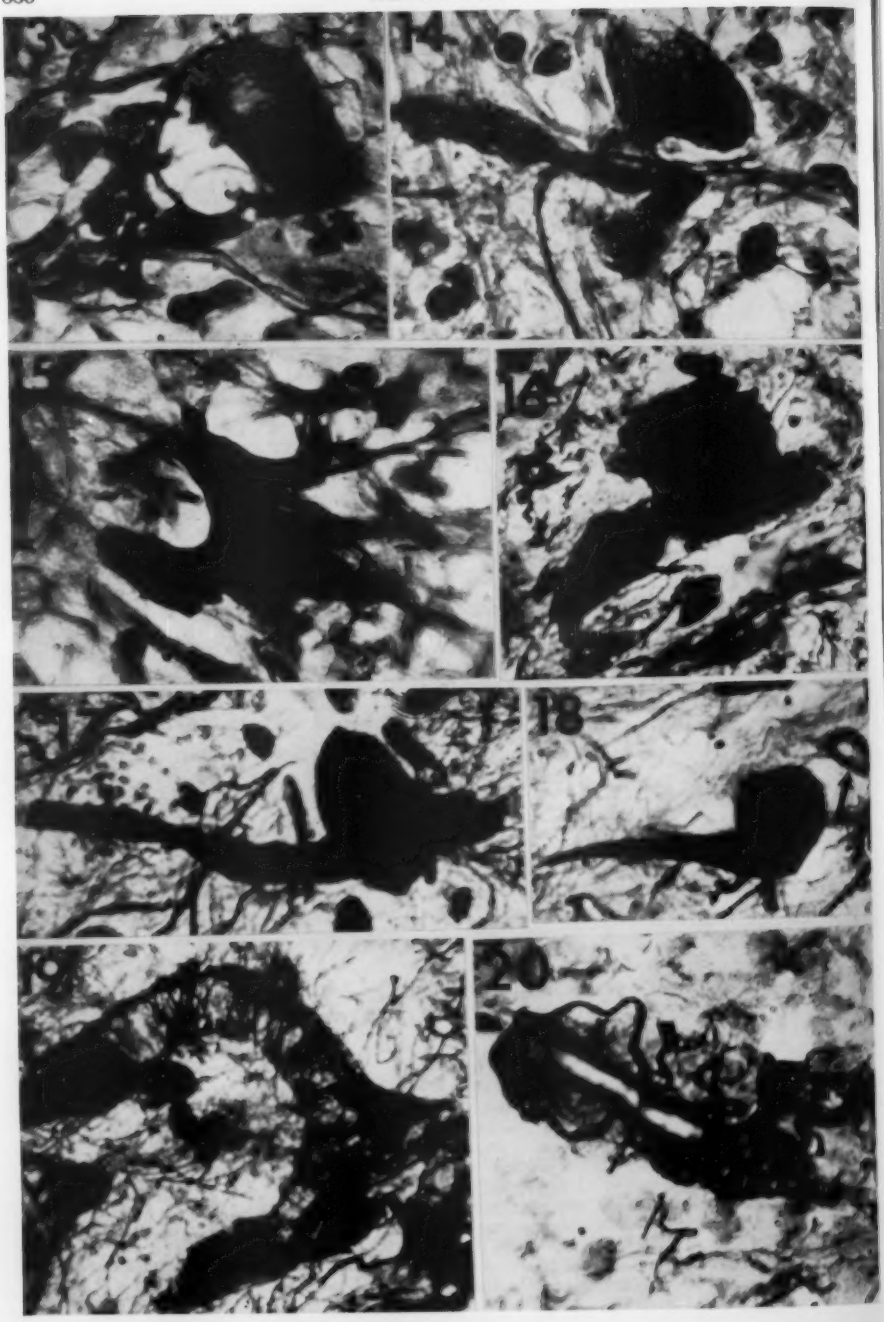
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FIG. 13. *Case 2.* Degenerated neurons with vacuolization of cell body (× 1,000)

FIG. 14. *Case 2.* A form of ganglion cell degeneration with peculiar bulb formation (× 1,000)

FIGS. 15-17. *Case 2.* Different types of neuronal degeneration

FIG. 18. *Case 2.* Degenerated neuron with homogeneously black impregnated body and fragmented processes. Ring formation (see arrow) represents remnants of disintegrated astroglia. (× 1,000)

FIG. 19. *Case 2.* Blood vessel from slightly damaged area shows distinctly the cells and processes of the perivascular structures. (× 1,000)

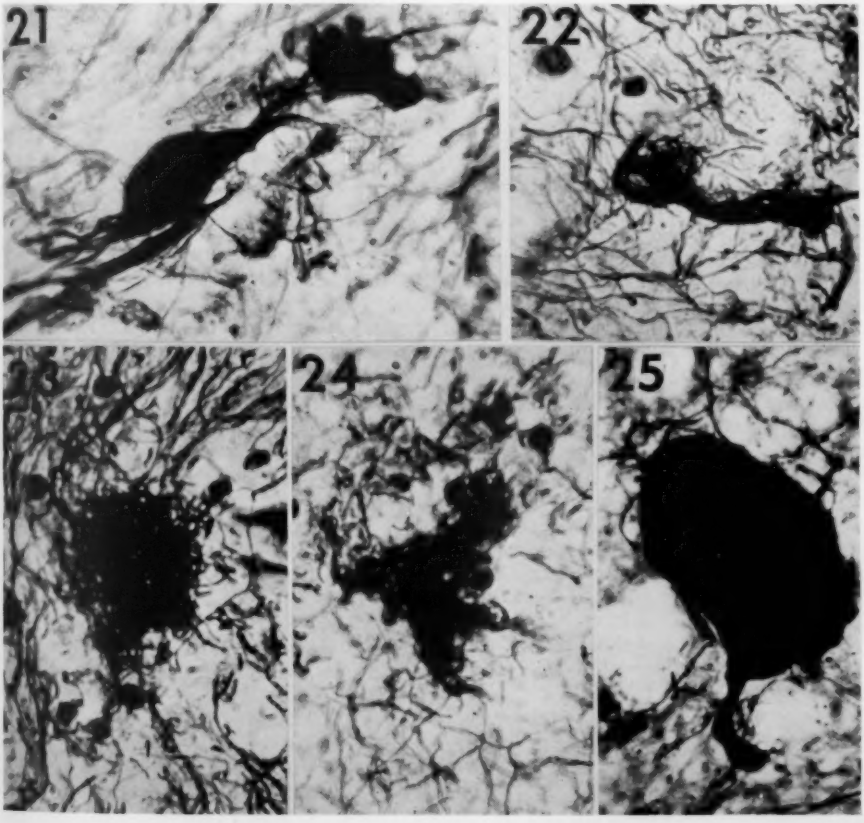
FIG. 20. *Case 2.* Blood vessel from severely damaged area shows absence of normal perivascular structures. Thickened glial fibers surround the blood vessel. (× 1,000)

FIG. 21. *Case 3.* Degenerated neuron with disintegrated, deeply impregnated cell body and markedly swollen process (× 1,000)

FIG. 22. *Case 3.* Neuronal degeneration similar to fibrillary degeneration of senile dementia (× 1,000)

FIGS. 23 and 24. *Case 3.* Peculiar forms of neuronal degeneration, in which only densely intertwined fine fibers can be distinguished (× 1,000)

FIG. 25. *Case 4.* Enlarged degenerated ganglion cell with homogeneously impregnated cell body and process (× 1,000)



abuse, regarded as secondary to their mental conditions. Case 3, with symptoms of delirium tremens had, pathologically, pronounced changes in the mammillary bodies with a peculiar fibrillary neuronal degeneration. The pathologic changes in Case 4 included swollen, degenerated neurons limited to the mammillary bodies.

The mammillary bodies, cerebellum, and corpus callosum have been described in the literature as the most probable site of pathologic changes in Korsakoff's psychosis, Wernicke's syndrome, and psychoses associated with alcoholism. However, specificity of the histopathologic changes associated with these clinical conditions, has not been reported. In the present 4 cases, the slides stained with conventional technics indicated pathologic changes such as loss of neurons, gliosis, neuronal degeneration, and vascular changes. These changes are in agreement with the findings described previously[5–10] and can be classified as nonspecific.

However, examination with silver carbonate suggests that the mammillary bodies are the site of peculiar forms of degeneration not encountered in other areas of the brain or in other pathologic conditions.

These changes can be summarized as [1] peculiar skein formations with the degenerated cell body in the center and concentrically arranged fragmented processes, [2] fine fibrillary degeneration of the neurons, and [3] enlarged, rounded degenerated ganglion cells.

The examination of 2 patients with Korsakoff's psychosis and 2 with psychosis partly attributed to alcoholic abuse may not constitute proof that these pathologic changes in the mammillary bodies of alcoholics are pathognomonic. However, since these are the only brains of alcoholics so far analyzed with silver carbonate preparations, future examinations with this technic may establish the histopathology of this clinical condition.

SUMMARY

Silver carbonate technics were used to examine degenerative changes in the brains of 4 alcoholic patients, 2 with Korsakoff's psychosis. The different types of histopathologic findings and their specificity are discussed.

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Chemical basis of the Marchi method for degenerating myelin

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THE MARCHI stain for demonstrating degenerating myelin is an empirical method, the fundamental chemistry of which is not well understood. The method depends upon the ability of formalin-fixed degenerating myelin to reduce osmium tetroxide in the presence of an oxidizing agent. Although normal myelin is unstained, the method is not specific for degenerating myelin because neutral fat also stains by this method.[1] In spite of the usefulness of the technic, relatively little has been done to elucidate its chemistry. In a series of recent studies on this problem, Wolman[2,3,4,5] has concluded that the responsible factor in the degenerating myelin may be a breakdown product of an acidic polysaccharide. The present study concerns the solubility of the Marchi material in some organic solvents and in water.

METHODS

Cats were used in most of the experiments although rats and chickens were also used with equal success. The sciatic nerves were aseptically sectioned bilaterally at the level of the greater trochanter of the femur. Degeneration was allowed to proceed fourteen to twenty days. At the end of this time, the animals were perfused under Nembutal anesthesia with 10% formalin through the left ventricle of the heart. The degenerated nerves were removed and placed in 10% formalin for two days.

The nerves were then dehydrated by freeze-drying and extracted in a Soxhlet apparatus with petroleum ether (Baker's reagent grade, 30 to 60° C. boiling range). Pieces were cut out of the nerves before freeze-drying, after freeze-drying and after freeze-drying and extraction. These pieces were stained in 2 changes of Swank-Davenport solution (60 cc. of 1% potassium chlorate, 20 cc. of 1% osmium tetroxide, 12 cc. of formalin, and 1 cc. of glacial acetic acid) for ten days and paraffin sections were prepared in the usual manner.

In analyzing the petroleum ether extracts for carbohydrates, ninhydrin and the acetylacetone reagent[6] were used to detect hexosamines; ammoniacal silver nitrate,[6] alkaline triphenyltetrazolium,[7] benzidine,[8] and m-phenylenediamine[9] were used as tests for reducing sugars. In the course of the investigation it was observed that p-dimethylaminobenzaldehyde[10] in normal hydrochloric acid (Ehrlich's reagent) gives a yellow-green color with glucosamine, glucosaminic acid, and heparin when the color is allowed to develop overnight.

Bromination of the tissues was done in 1% bromine water after formalin fixation. The blocks of tissue were then washed in distilled water for twelve hours and put in the Swank-Davenport solution.

RESULTS

Formalin-fixed, frozen-dried degenerated nerves show a total loss of Marchi material after extraction with petroleum ether (Figs. 1 and 2). In addition to the Marchi material from the degenerated myelin, all of the neutral fat is extracted from adipose tissue in the connective tissue sheaths of the nerves. This neutral fat also gives the Marchi reaction because its constituent unsaturated fatty acid esters are able to reduce the osmium of the Swank-Davenport solution.

There are reasons for believing that the Marchi material in the myelin is not neutral fat since Johnson and associates[11] have shown that neutral fat is not increased in wallerian degeneration. Furthermore, we have observed

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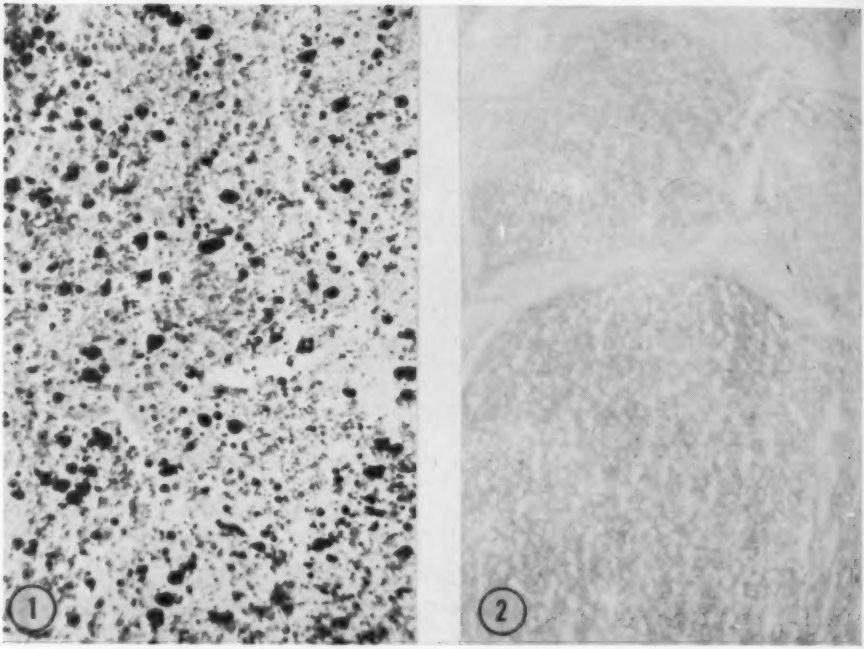

FIG. 1. Cross section of a portion of a 16-day degenerating cat sciatic nerve after freeze-drying and staining by the Swank-Davenport method. A large amount of Marchi material is present. (×100)

FIG. 2. Same as in Figure 1 except that this nerve was extracted with petroleum ether after freeze-drying and before being placed in the Swank-Davenport fluid. The petroleum ether has completely extracted all of the Marchi material. (×100)

TABLE 1
CARBOHYDRATE TESTS

	Heparin	*Glucosamine*	*Glucosaminic acid*	*Degenerating sciatic extract*
Ninhydrin	+	+	+	—
Ammoniac silver nitrate	—	+	+	—
Benzidine	+	+	—	—
Acetylacetone	—	+	+	—
m-Phenylenediamine	—	+	—	—
Alkaline triphenyltetrazolium	+	+	+	+
p-Dimethylaminobenzaldehyde	+	+	+	—

that if the chlorate concentration in the Swank-Davenport solution is increased from 0.64% (final concentration) to 3.2%, the neutral fat will still reduce the osmium in the fluid but the degenerated myelin will not. Bromination of the tissue before staining in the Swank-Davenport solution abolishes the Marchi reaction both in the neutral fat and in the degenerating myelin. In the case of the fat, this is due to bromination of the olefin bonds, and

the same explanation seems likely for the degenerating myelin.

Both the fat and the Marchi material of the degenerating myelin are extremely soluble in petroleum ether, and the extracts of 6 degenerating cat sciatic nerves could be concentrated to a few cubic centimeters without any precipitation of the dissolved material. These concentrated petroleum ether extracts were separated into 2 fractions by the addition of 10 volumes of ice cold acetone. The acetone insoluble material could reduce 1% osmium tetroxide but not the Swank-Davenport fluid. The acetone soluble material, which was also insoluble in water, reduced the Swank-Davenport solution. This fraction was taken to dryness in vacuo and redissolved in 1 cc. of petroleum ether and drops were applied to disks of filter paper for the carbohydrate tests.

Twenty microgram samples of heparin, glucosamine, and glucosaminic acid were used as controls because Wolman is of the opinion that a compound such as glucosaminic acid is responsible for the Marchi reaction in degenerating nerves. The results are summarized in the table. The degenerating nerve extracts containing the Marchi material reduced alkaline triphenyltetrazolium but reacted negatively in all other tests for carbohydrates. Tetrazolium is also reduced by a similar extract of neutral fat, and it has been pointed out that some fat is unavoidably present in the degenerating nerve extracts.

While we cannot exclude the possibility that a polysaccharide may be present in myelin, we find no evidence to support Wolman's hypothesis that a carbohydrate is the factor responsible for the Marchi reaction in degenerating myelin. The solubility of the Marchi material in petroleum ether and cold acetone, together with its well-known insolubility in water, suggests that it is a lipid. If so, the possibility of its being neutral fat can be discounted. Of all the myelin lipids, the Marchi material most closely resembles cholesterol in its solubility in both acetone and petroleum ether.

ADDENDUM

After this paper was presented, an excellent investigation of the physicochemical properties of the Marchi material was published by Adams.[12] On the basis of an earlier observation by Hurst that the Marchi material is soluble in acetone, Adams rejected Wolman's hypothesis that a carbohydrate is involved. Furthermore, he observed that prior bromination of degenerating myelin prevents the Marchi reaction. Our results confirm both of these points. In addition, Adams presented evidence to show that normal myelin is hydrophilic while degenerating myelin is hydrophobic. Osmium tetroxide is soluble in both normal and degenerating myelin, but chlorate is not soluble in hydrophobic degenerating myelin. As a result, chlorate oxidizes the olefin bonds in normal myelin but the bonds are oxidized by the osmium alone in degenerating myelin. Interestingly enough, Adams suggests that cholesterol oleate is the hydrophobic compound in degenerating myelin. This would agree with our solubility studies.

Our observation that neutral fat, but not degenerating myelin, is stained when the chlorate concentration is increased to 3.2% would seem to indicate that neutral fat is more hydrophobic and that chlorate, even at high concentrations, is unable to penetrate it.

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Diagnostic value of Horner's syndrome in thrombosis of the carotid artery

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THE DEFINITIVE DIAGNOSIS of carotid artery thrombosis is best made by arteriography.[1] The physical examination has been of little help in this regard, except for a few cases in which ipsilateral optic atrophy or central retinal artery occlusion exists in combination with a contralateral hemiparesis or sensory loss.[2] Palpation of the common carotid artery in the neck or the internal carotid artery in the pharynx has proved to be unreliable,[3] and compression of the common carotid artery on the side opposite the suspected thrombosis may produce syncope.[4] Syncope, however, may also result from this maneuver in basilar artery insufficiency and thrombosis of the anterior cerebral artery.[4]

An analysis of 18 cases of proved carotid thrombosis examined in the last two years reveals that an ipsilateral Horner's syndrome was present in 12. Most recent reviews of carotid thrombosis do not report this finding,[5] although a few mention a fleeting ipsilateral miosis or an occasional ptosis among the ophthalmologic manifestations.[6,7] Siegert,[8] in 1938, noted the occurrence of miosis on the side of the thrombosed vessel. In an extensive review, Milleti[9] reported ipsilateral miosis in 7 of 44 cases, interpreted this phenomenon to be due to involvement of the sympathetic plexus about the carotid vessels, and indicated that this finding was of diagnostic value. Johnson and Walker[10] reported miosis in 10 patients and ptosis in 6. Walsh[11] describes a case of internal carotid thrombosis with an ipsilateral Horner's syndrome.

It is our experience that an incomplete Horner's syndrome on the side of the thrombosis is more frequent than the literature indicates, and we have found it diagnostic in that it is possible to differentiate between middle cerebral and internal carotid artery thrombosis by the presence of this syndrome. It is also possible to differentiate intracerebral brain tumor and internal carotid thrombosis when a partial Horner's syndrome is present on the side opposite the hemiplegia.

If the recently proposed measures for treatment of internal carotid thrombosis by surgery[12] or anticoagulants[13] are to be effective, it is important to make an early diagnosis.

Several cases will be presented which illustrate Horner's syndrome in association with occlusion of the carotid system at different levels – from the common carotid artery in the neck to the bifurcation of the internal carotid artery.

REPORT OF CASES

Case 1. A 59-year-old, right-handed man was admitted because of sudden onset of aphasia and right hemiparesis. He had had 2 similar attacks within the year before admission. Examination revealed ptosis of the left lid; left miosis (3 mm. as compared to 6 mm. on the right), and absence of sweating on the left side of the face.

General physical examination and chest x-ray were normal. A left carotid arteriogram demonstrated complete occlusion of the common carotid artery (Fig. 1). Exploration of the left common carotid artery revealed a thrombus beginning 2 cm. proximal to the bifurcation. The artery was opened, and the clot was followed for several centimeters into the external carotid and to the base of the skull in the internal carotid artery.

Comment. In this case, the thrombosis involved the external as well as the internal carotid artery; anhidrosis was present in addition to miosis and ptosis.

Case 2. A 45-year-old, right-handed mechanic was admitted because of the second episode, within a month, of aphasia and right hemiparesis. Examination disclosed complete expressive-receptive aphasia and right hemiplegia. The left pupil

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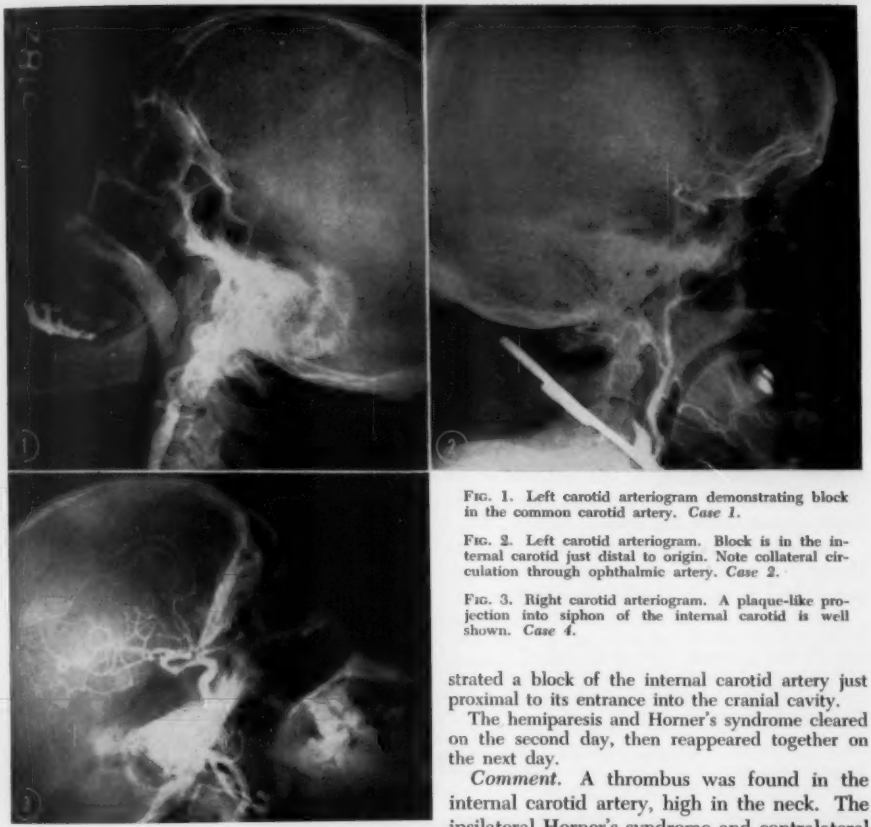

FIG. 1. Left carotid arteriogram demonstrating block in the common carotid artery. *Case 1.*

FIG. 2. Left carotid arteriogram. Block is in the internal carotid just distal to origin. Note collateral circulation through ophthalmic artery. *Case 2.*

FIG. 3. Right carotid arteriogram. A plaque-like projection into siphon of the internal carotid is well shown. *Case 4.*

was smaller than the right, but both reacted to light. There was a slight left ptosis.

The general physical examination and chest x-ray were normal. A left carotid arteriogram revealed occlusion of the internal carotid artery close to its origin, with some filling of the siphon via external carotid-ophthalmic anastomosis (Fig. 2). This thrombosis was confirmed at thromboendarterectomy.

Comment. Thrombosis of the internal carotid artery just distal to its origin was associated with a partial Horner's syndrome.

Case 3. A right-handed lawyer, aged 42, suffered a sudden headache and right-sided weakness. No history of previous attacks was elicited. Examination revealed a partial expressive-receptive aphasia and a mild right hemiparesis. Definite left ptosis and miosis were present.

General physical examination and chest x-ray were normal. A left carotid arteriogram demonstrated a block of the internal carotid artery just proximal to its entrance into the cranial cavity.

The hemiparesis and Horner's syndrome cleared on the second day, then reappeared together on the next day.

Comment. A thrombus was found in the internal carotid artery, high in the neck. The ipsilateral Horner's syndrome and contralateral hemiparesis disappeared and reappeared together.

Case 4. A 56-year-old, right-handed housewife presented with complaints of confusion and weakness of the right leg of sudden onset. Two years previously, there had been a transient left hemiparesis. Examination revealed slight weakness of the right leg. The deep tendon reflexes were faster on the left, and a Babinski sign was present on the left. There was a ptosis of the right lid and a miotic pupil in the right eye. General physical examination revealed a grade II systolic murmur at the apex, and a chest x-ray showed enlargement of the left ventricle. Bilateral carotid arteriography demonstrated normal circulation on the left but a distinct narrowing in the carotid siphon on the right (Fig. 3).

Comment. Despite weakness of the right leg on admission, a right-sided lesion was suspected because of Horner's syndrome.

Case 5. A 65-year-old, right-handed man was admitted after he suffered a sudden aphasia. Examination revealed mild facial weakness and a Babinski sign on the right side. There was a left ptosis and miosis. The aphasia gradually improved, and he was discharged.

One month after leaving the hospital, he suddenly became completely aphasic and paralyzed on the right side. Examination disclosed a right hemiplegia with a left ptosis and miosis. General physical examination revealed normal blood pressure, but the pulse was 50. The patient sank into coma and developed Cheyne-Stokes respirations. The left pupil gradually dilated until it was larger than the right and failed to react to light. A left carotid arteriogram showed an occlusion at the bifurcation of the internal carotid artery. Injection of the right carotid artery demonstrated a normal right circulation with some dye entering the right anterior cerebral artery. The patient died ten days after arteriography.

Comment. In this case, an occlusion high in the internal carotid artery produced persistent Horner's syndrome. With the appearance of signs of brain-stem compression, the miotic pupil became large and fixed.

The following patient is one of two who had Horner's syndromes with contralateral hemiparesis and no arteriographic abnormalities.

Case 6. A 45-year-old, right-handed woman suddenly became aphasic and weak on the right side. Examination revealed expressive-receptive aphasia and a right hemiparesis with hemihypesthesia. There was left miosis and absence of sweating on the left side of the face.

General physical examination disclosed a blood pressure of 200/100 mm. Hg and a grade II systolic murmur. The chest x-ray showed prominence of the left ventricle. A left carotid arteriogram was completely normal.

This patient made a good recovery, regaining some power of speech and good use of the right extremities.

Comment. Ptosis was absent and anhidrosis was present in this and in the other patient with normal arteriographic studies.

DISCUSSION

The table summarizes 18 cases of carotid artery thrombosis proved by arteriography and surgery. Ipsilateral Horner's syndrome was observed in 12 patients whose lesions represented different levels of carotid occlusion, as indicated in the case reports. Anhidrosis was present in 1 patient (case 1) in whom the thrombus was found in the external as well as the internal carotid artery. None of the other patients with thrombosis restricted to the internal carotid had a sweating disturbance.

According to Jaffe and associates,[14,15] the sympathetic fibers concerned with facial perspiration leave the pupillary fibers at the bifurcation of the common carotid artery and follow the external carotid artery and its branches. Therefore, as one would expect in thrombosis of the internal carotid artery, Horner's syn-

CAROTID ARTERY THROMBOSIS IN 18 PATIENTS VERIFIED BY ANGIOGRAPHY AND SURGERY

Case	*Horner's syndrome*	*Results of arteriogram*	*Surgery for thrombus*
O. R.	Partial	Thrombosis in neck above bifurcation	Thromboendarterectomy
R. R.	Partial	Not done	Clot found in internal carotid artery above bifurcation at surgery
D. T.	Partial	Thrombosis of internal carotid artery in neck above bifurcation	Thromboendarterectomy
G. T.	Absent	Thrombosis of internal carotid artery in neck	None
W. R.	Partial	Thrombosis of internal carotid artery in neck	None
P. L.	Absent	Thrombosis of internal carotid artery at siphon	None
S. W.	Complete	Thrombosis at common carotid artery	Thromboendarterectomy
K. H.	Partial	Clot in bifurcating of common carotid artery	Thromboendarterectomy
R. C.	Absent	Clot in carotid siphon	None
E. A.	Absent	Thrombosis in internal carotid artery above bifurcation of common carotid artery	None
G. A.	Partial	Thrombosis at bifurcation of common carotid artery	None
P. G.	Absent	Thrombosis above bifurcation in neck	Thromboendarterectomy
H. C.	Partial	Thrombosis above bifurcation with collateral filling of internal carotid intracranial artery	Thromboendarterectomy
C. F.	Absent	Thrombosis at bifurcation in neck	Thromboendarterectomy
H. R.	Partial	Thrombosis in carotid siphon	None
M. M.	Partial	Thrombosis in carotid siphon	None
P. W.	Partial	Bifurcation of internal carotid artery	None
B. H.	Partial	Bifurcation in neck	Thromboendarterectomy

drome was incomplete, ptosis and miosis being the prevalent signs.

McGuire and Jaeger[16] state that ipsilateral Horner's syndrome is present when the intracranial portion of the internal carotid artery is thrombosed. However, we have noted ptosis and miosis in several cases in which the thrombi were located in the internal carotid artery in the neck. Therefore, the presence of Horner's syndrome does not necessarily restrict the location of the thrombus to the intracranial portion of the artery.

In some patients, the sympathetic lesion was manifested by a slight difference in pupillary size and a minimal droop of the upper lid. These findings are easily missed unless specifically sought in the examination, and repeated observations are often necessary.

The etiology of the sympathetic disturbance in occlusion of the carotid system is not clear. The evidence favors a concept that ischemia of the sympathetic neurons of the third order may occur, caused by decreased blood flow through vasa nervorum arising from the carotid artery. The transient nature of the eye signs, paralleling other signs of carotid insufficiency (case 3), suggests that the sympathetic disturbance and the hemiplegia have similar causes. It is unlikely that Horner's syndrome is caused by inflammatory involvement of sympathetic fibers in the wall of the thrombosed vessel, as hypothesized by Milleti. An organic occlusion could not be demonstrated in two patients who had complete Horner's syndrome and contralateral hemiplegia.

At present, a 65-year-old man, who is subject to recurrent weakness of the left arm in company with a recurrent right ptosis and miosis, is being observed. Arteriography outlined patent carotid systems bilaterally. We believe the findings in this case are best explained by periodic carotid insufficiency affecting both the cervical sympathetic network and the right cerebral hemisphere. A histologic study of the cervical sympathetic ganglia and their branches in cases of carotid thrombosis is in progress and may be of value in discovering the mechanism of Horner's syndrome in this disease.

SUMMARY

1. Ipsilateral Horner's syndrome was observed in 12 of 18 patients with verified carotid thrombosis. Anhidrosis was present in only 1, in whom the thrombus involved the common and external carotid arteries.

2. Horner's syndrome was present at all levels of occlusion of the internal carotid artery.

3. Arteriograms were normal in 2 patients with miosis, anhidrosis, and contralateral hemiparesis.

4. It is suggested that the sympathetic disturbances observed in this series are due to ischemia mediated through the vasa nervorum.

5. Ptosis and miosis in association with contralateral hemiparesis or other neurologic deficit suggest an occlusion of the internal carotid artery on the side corresponding to the eye signs. If anhidrosis is also present, either the common and external carotid arteries are involved or no lesion can be demonstrated.

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Modified pendulousness test to assess tonus of thigh muscles in spasticity

Miklós Boczko, M.D., and Marco Mumenthaler, M.D.

EVALUATION OF MUSCLE TONUS is difficult if only the usual subjective interpretation based on passive movements of the extremities can be used. Wartenberg[1,2] described the so-called pendulousness test of the legs as an advantageous method of studying tonus conditions in the thigh muscles. By modifying this test, a clinically applicable method of recording muscle tonus was devised.

METHOD

The patient sits on the edge of a table with legs hanging freely in an almost completely darkened room (Fig. 1). The leg to be examined is held in position by a board that rests against the back of the ankle. This support enables the knee joint to be held at an angle of approximately 45°. An electric light fed by a battery is fastened to the big toe. The board is then removed from behind, allowing the leg to swing freely. The small light marks the leg movements, which are recorded by a camera suspended at a constant distance (120 cm.) above the leg. The camera slowly describes an arc of approximately 60°. The plane of movement of the camera is perpendicular to the plane of motion of the leg. The swinging movements of the light are recorded on a film in the camera so as to form a more or less sinusoidal curve. The rotation speed of the camera is known (one complete arc movement of 60° lasting 12 seconds). Figure 2 shows a normal record made by the method described. The text of the illustration explains the method of evaluating the tracings. The rotation speed of the camera being known, the over-all swinging time of the leg can be deduced.

MATERIAL

A total of 28 records was obtained in 6 healthy persons, and 86 records were made in 13 patients with spastic paralysis of the lower extremity. Another 24 records were made in patients with spasticity after treatment with an antispastic drug, Ciba 13.155. All 13 patients had distinct clinical signs of spastic paralysis of one or both legs, with characteristic tonic distribution of the Wernicke-Mann type. Degree of spasticity was severe in 4, distinct in 5, and moderate in 4 patients.

RESULTS

Records were evaluated as follows:

1) Qualitative aspects – regularity of the swinging process, normal sinusoidal in contrast to abnormal arched or looping progress of the tracing, and other possible irregularities.

2) Quantitative properties – the total wave count; over-all swinging time; amplitude of the first backswing (A_1); and extent of braking during the first pendulous movement, that is, the relation of A_1 to the difference between A_1 and the amplitude of the first forward swing (A_2).

The normal record always corresponds more or less to that shown in Figure 2. Sinusoidal progress, lack of loops, and brisk changes in direction of the tracing are characteristic. As a rule, healthy subjects have 6 to 7 waves but never less than 5. In some instances, the entire pendulous movement lasted more than 12 seconds. In such cases, therefore, the record does not contain the sixth and subsequent waves.

Of the patients with spasticity, 15% had records similar to those of healthy subjects (Fig. 3). The rest had characteristic deviations. Arches and loops were seen most frequently (Figs. 4 and 5). Both are the outcome of lateral displacement, that is, deviation of the spastic leg from the sagittal plane while swinging. Arches are caused by side

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In memoriam Robert Wartenberg.

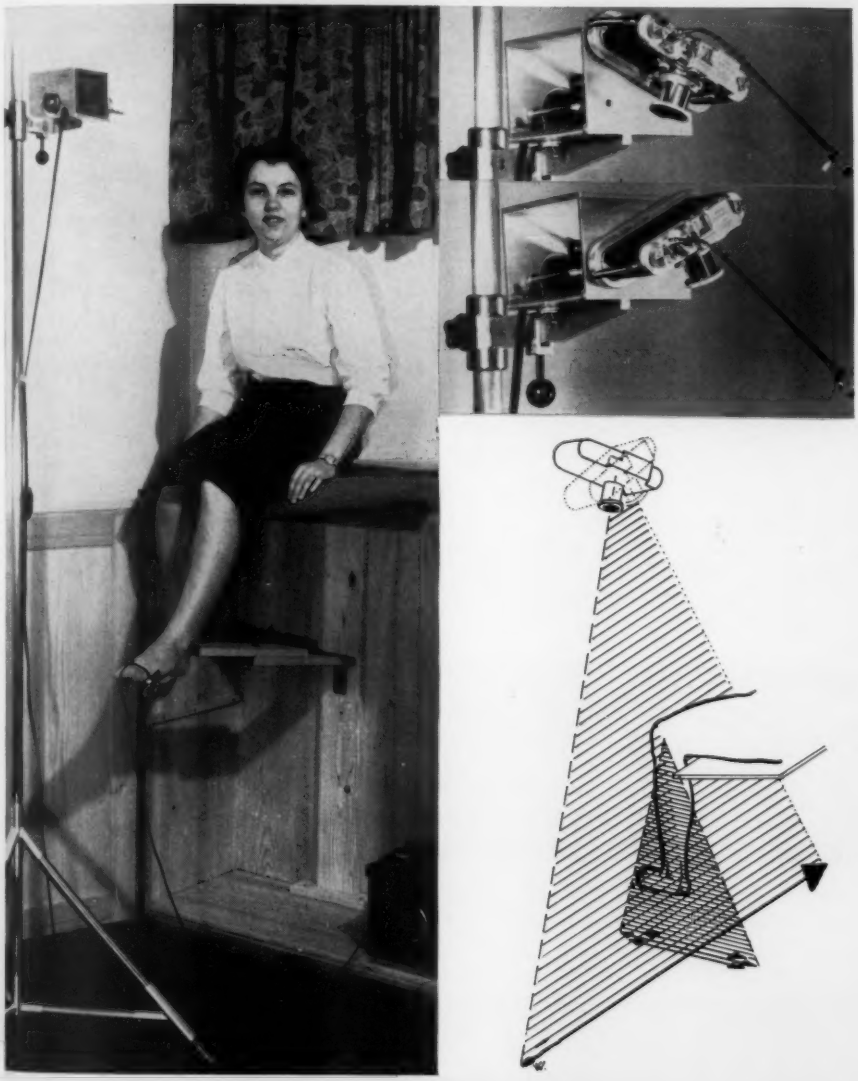
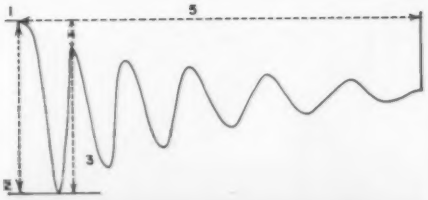


FIG. 1. Test room and instruments. The patient sits on the edge of a table with the left heel supported by a board so that the knee is flexed at an angle of approximately 45°. Note the electric light attached to the big toe and fed by the battery below. The camera, moved by the motor behind, can be better seen on the enlarged photos (top corner). These show the starting (upper photo) and end points (lower photo) of the rotation movement of the camera. The duration of this movement is 12 seconds.



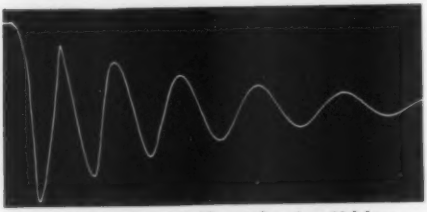


FIG. 2. Normal record. The regular, sinusoidal form of the tracing is characteristic. [1] Base line: represents height of leg before support is removed; [2] amplitude of first backswing (A_1); [3] amplitude of first forward swing (A_2); [4] amplitude difference (A_1-A_2); and [5] over-all swinging time (in distance units): from the beginning of swinging, that is, end of base line, to the highest point of the last—as to degree of size—evaluable forward swing. The first wave (first backswing and first forward swing) is represented by that part of the tracing situated between the end point of the base line and the subsequent highest point of the curve. The remaining waves can be counted accordingly. Number of waves in the tracing above is 6.

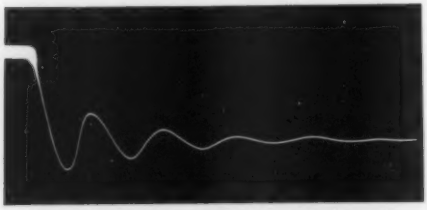


FIG. 3. Record of a spastic patient. Qualitatively, the tracing is similar to that of the healthy individual. Quantitatively, however, diminution in the size of waves, which is more pronounced in the first forward swing, is observed. The over-all swinging time and total wave count are greatly reduced.

FIG. 4. Record of a spastic patient. Qualitative deviation from the normal consists of loop and arch formations.

movements in the same direction as that of the camera, and loops result when movements proceed in the opposite direction. In some cases, a sudden, jerky, extension movement was observed as the leg was making the first backswing. This movement was shown on the tracing as a brief interruption in the first backswing followed by a forward swing of short duration, the original backswing then reasserting itself (Fig. 5). Repeated extension jerks sometimes distort the record to the extent that quantitative evaluation is impossible.

In 69 of 71 records of patients with spasticity, the number of swings was limited to 5 or less. The waves could not be counted in 2 severely spastic patients because of jerky movements. The mean value of the total wave count in healthy individuals was 5.64, with a mean error of $\pm$ 0.04; corresponding figures in spastic patients were 3.9 and $\pm$ 0.45, respectively $\left(M = X \pm 2 \frac{\sigma}{\sqrt{n}}\right)$.

The swinging time was never less than 9.5 seconds in 28 tests in healthy subjects. In contrast, the swinging time lasted longer than 9.5 seconds in only 3 of 71 tests in patients with spasticity. The mean value for healthy subjects was 10.82 seconds, with a mean error of $\pm$ 0.47. Corresponding values in patients with spasticity were 7.09 and $\pm$ 2.89, respectively $\left(M = X \pm 3 \frac{\sigma}{\sqrt{n}}\right)$.

Since the distance between the camera and the light attached to the big toe is kept constant at 120 cm., the amplitude of the first backswing represents a measurable and comparable value. Usually, in healthy subjects, it lies at 12 mm. or more. Less than this value was noted in only 1 of 28 normal records.

FIG. 5. Record of spastic patient. On first backswing, brief forward swing corresponds to interruption of free pendulous movement by sudden extension jerk.

In 71 spastic records, A_1 was found on only 3 occasions to be greater than 12 mm., the remainder displaying less. The mean value was 14.09, with a mean error of $\pm$ 0.31, in healthy persons and 9.33, with a mean error of $\pm$ 0.88, in spastic patients

$$(M = X \pm 3 \frac{\sigma}{\sqrt{n}}).$$

By amplitude ratio is meant the relation of A_1 to the difference $(A_1 - A_2)$. This ratio indicates, in a sense, the braking effect to which the first swinging is subjected. Normally, the amplitude ratio was more than 5, except in 2 instances, when values of 4.91 and 4.45, respectively, were obtained. In diseased subjects, the ratio was less than 5 in 69 of 71 cases, whereas values of 6 and 7.28, respectively, were recorded in only 2 cases. The normal mean value was 6·41, with a mean error of $\pm$ 0.63. In patients with spasticity, the mean value was 2.61, with a mean error of $\pm$ 0.40 $(M = X \pm 3 \frac{\sigma}{\sqrt{n}})$.

The above facts and figures on the evaluation of the pendulousness test seem to prove that this method offers distinct possibilities for the recording of qualitative as well as quantitative differences between healthy subjects and patients with spastic paralysis of the lower extremities. Furthermore, to test the usefulness of the method in the assessment of quantitative differences among patients with varying degrees of spasticity, records of severely and distinctly spastic patients were compared. Table 1 demonstrates that this quantitative differentiation is possible, the difference between the 2 groups regarding over-all swinging time and amplitude ratio being significant.

The quantitative assessment of spasticity can be of practical importance in the clinical study of drugs influencing muscle tonus and spasticity. The practicability of the pendulousness test for such purposes was tested using a drug with antispastic properties, Ciba 13.155. Intravenous injection of 0.5 to 1 mg. per kilogram of body weight was done in 7 spastic patients. The pendulousness test was performed

TABLE 1

QUANTITATIVE DIFFERENCES BETWEEN DEGREES OF SPASTICITY AS BORNE OUT BY THE PENDULOUSNESS TEST

Degree of spasticity	*Number of patients*	*Number of tests*	*Maximum and minimum values*	
			Over-all swinging time in seconds	*Amplitude quotient*
Distinct	5	46	7.01 to 5.65	5.52 to 3.48
Severe	4/2*	23/7*	5.15 to 3.67	1.713 to 1.707

*In 7 records of 2 patients, only the over-all swinging time is shown. Other quantitative measurements were impossible because of distortion of the tracings by qualitative deviations.

TABLE 2

QUANTITATIVE DIFFERENCES IN THE PENDULOUSNESS TEST BEFORE AND AFTER INTRAVENOUS ADMINISTRATION OF AN ANTISPASTIC DRUG

Name	*Clinical improvement*	*Number of tests*		*Improvement*		
		Before injection	*After injection*	*Over-all swinging time in seconds*	*Amplitude quotient*	*Qualitative deviations*
W. H.	+	5	6	Significant	Significant	
L. H.	+	4	4		Significant	
N. A.	+	5	3			Significant
S. F.	+	4	4			
H. R.	—	4	3			
K. H.	—	4	4			
T. C.	Evaluation impossible for technical reasons					

before and one-half hour after injection. The results can be seen in Table 2. Although the spasticity of 4 of the patients was considered to be lessened clinically, the difference between the records before and after injection was significant in only 3. The records, although not normal after injection, did show a shift in that direction. As expected, there was no significant change in the tracings after injection in 2 other patients who showed no clinical improvement. Technical failure prevented evaluation of the records of the seventh patient.

COMMENT

Wartenberg originally based his interpretation of the test on a visual, qualitative impression. The only quantitative datum he considered was the number of swings. Concerning spastic conditions, Wartenberg states: "If there is any change, it lies more in quality than in quantity." On alterations in extrapyramidal rigidity, he says: ". . . changes are quantitative only."

Increase of tonus, whatever the cause, reduces the free swinging of the extremity in question. Our examinations confirm that, in every case, quantitative differences between healthy subjects and patients with spastic paralysis exist in the free swinging of the leg. The amplitude of the swings and the over-all swinging time of the spastic leg are reduced. The qualitative deviations from normal in spastic conditions, stressed by Wartenberg, were found in only 85% of the cases.

In accordance with Wartenberg's findings, the pendulous movement of the spastic leg does not usually occur only in 1 plane (sagittal), but in 2 (sagittal and frontal). This represents a difference not only from healthy persons but, according to Wartenberg, also from patients with extrapyramidal rigidity. Thus, the diagnostic importance of this factor should not be neglected. As to the range of the first swing of the leg, Wartenberg[1] says: "On the backward movement the heel does not swing back as far as in the normal; this occurs when the tonus of the extensor muscle of the knee is greater than that of the flexors, as in spastic paralysis." Further, "In pyramidal spasticity . . . the forward movements are brisker than the backward, and the range of the backward movement is diminished." According to our findings, the amplitude of the first backswing (A_1) as well as that of the subsequent first forward swing (A_2) is reduced. (The tables do not contain the values for A_2.) The sudden, jerky, extension movements superimposed on the first backswing have already been discussed. In no case is the diminution of the back- and forward swings equal. In patients with spasticity, the amplitude of the forward swing is more markedly decreased. This is borne out by the diminished amplitude ratio (A_1/A_1-A_2). The braking effect of spasticity, that is, the tonus increase in the flexor muscles of the knee joint, outweighs that of the extensors. These statements are based on repeated examinations of 13 patients who had characteristic preferential spastic tonus distribution, wherein the extensor tonus of the thigh muscles predominated.

This reversal of the tonus distribution in the knee joint is only the result of the position of the patient during the pendulousness test. As is known, there is a change in tonus distribution of the extremities corresponding to the position of body in space.[3] Foerster[4] demonstrated that the proprioceptive impulses of the muscles influence the excitability of spinal motoneurons. Excitability diminishes in the motoneurons of continuously stretched muscles, whereas the opposite is true in motoneurons of continuously shortened muscles. From this can be inferred that the prolonged flexed position of the knee joint in the sitting patient during the pendulousness test results in a greater amount of tonus increase in the flexor than in the extensor muscles of the thigh.

PRACTICAL APPLICATION OF THE TEST

When assessing test results, calculation of all the data mentioned above is not always necessary. The amplitude ratio definitely is the most reliable quantitative guide. For clinical purposes, calculation of the mean value of the amplitude ratio derived from 5 tracings of any one patient is sufficient.

The quantitatively assessed pathologic alterations in the tracings sometimes were supported by qualitative peculiarities. However, in this material, there was no record of qualitative changes not accompanied by quanti-

tative ones. Of course, the possibility that this occasionally could be the case should not be excluded.

This method has not yet been applied in patients with slight spasticity. A sufficient number of tests in patients with extrapyramidal, cerebellar, and other disturbances to which the application of the method has already been extended by Wartenberg,[1] also is lacking. In a smaller series, the impression was given that the method indicated can demonstrate smaller changes of tonus, for example, those resulting from antispastic drug treatment.

Currently, no similar test to record tonus conditions of the arm muscles is available. Presumably, the above method could be applied to the upper extremities once a position that allows the arm to swing freely is found.

SUMMARY

A method by which the tonus of the thigh muscles can be studied and quantitatively assessed is described. For that purpose, movements of the freely swinging leg are photographically recorded. Records of 13 patients with spastic paralysis of the lower extremities were significantly different from those of 6 healthy subjects. Similarly, severe spasticity could be differentiated from spastic hypertonus of a lesser degree. The method was found suitable to demonstrate the effects that lissive agents exert on spasticity.

Our best thanks are due to Dr. A. Bischoff for helpful advice and Mr. W. Gehret for technical assistance in preparing photographs of the records.

We are indebted to Ciba, Ltd. for putting a trial quantity of Ciba 13.155 at our disposal and also for generous financial support.

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Conservative vs. surgical treatment of cerebral aneurysms

D. Frank Benson, M.D.

SINCE THE INTRODUCTION of cerebral angiography in 1934[1] and the subsequent development of vascular surgery of the cranial vessels, intracranial aneurysms have come to be considered a surgical problem. Some neurosurgeons state that all proved aneurysms of the cerebral vessels deserve definitive surgical therapy unless there is definite medical contraindication.[2,3] Despite an accepted 14% mortality rate in surgical attack of intracranial aneurysms,[5] the neurosurgeon can honestly follow this dictum because of the known grave prognosis of intracranial bleeding. A commonly accepted rule is that about one-half of patients presenting with subarachnoid hemorrhage will die of the initial attack and one-fourth will succumb to recurrent bleeding. In the face of this type of prognosis, even a 14% mortality rate in surgical treatment looks good. It is the purpose of this paper to study the prognosis in conservatively treated cases of intracranial aneurysms.

STATISTICS

Statistics are notoriously misleading, and those used in most studies of intracranial aneurysms belong in this category. Intracranial bleeding is an unfortunately common occurrence, and mountains of statistics are available. Walton[4] lists 1,480 cases of subarachnoid hemorrhage taken from the literature, all with long-term follow-up. Mount[5] lists 469 surgically treated aneurysm cases. In recent years, many studies, most of them concerned with operative procedure and prognosis, have appeared.[3,6,7] In studying these statistics, several discordant points are noted:

- The conservatively treated group includes patients whose diagnoses fall within the rather broad boundaries of subarachnoid hemorrhage; whereas, the surgically treated group includes only those patients with proved aneurysms. The 2 categories are then compared. While 50 to 75% of cases of subarachnoid hemorrhage are due to aneurysms,[8,9] the two certainly cannot be used as equivalents.
- There are practically no reports of prognoses of patients with proved aneurysms who do not undergo surgery.

There are several rather obvious reasons for the above mentioned points. A given case of bleeding must be labeled subarachnoid hemorrhage until a more specific diagnosis can be made. There are only 2 common ways to make this diagnosis — angiography or autopsy. Most cerebral angiography is done by neurosurgeons, and the discovery of an aneurysm in the cerebral vascular tree immediately marks the patient as a potential candidate for surgery. In 1951, discussing intracranial aneurysms, Poppen[3] stated: "Conservative treatment is justifiable only in a few instances such as in bilateral multiple intracranial aneurysms, arteriosclerotic saccular aneurysms with minimal symptoms, arteriosclerotic aneurysmal dilatations that have produced no serious local symptoms and in cases in which inadequate collateral circulation prevents either direct or indirect attack."

- Lack of statistics on nonoperative treatment attests to the thoroughness of the surgical attack. We are faced with a situation in which there are relatively few conservatively treated cases, and these are far from representative.

Several studies from the recent literature,

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Weir Mitchell lecture, read at the Tenth Annual Meeting of the American Academy of Neurology, Philadelphia, April 24, 1958.

The author wishes to thank Henry W. Newman, M.D., for encouragement and Mrs. Mary K. Hellen for assistance in the patient follow-up.

TABLE 1
TIME OF DEATH AFTER INITIAL HEMORRHAGE

	Surgically treated cases	*Conservatively treated cases*
0 to 1 month	2	3
1 to 2 months	2	4
2 to 3 "	2	
1 to 2 years	2	
2 to 3 "		1
7 to 8 "		1

however, do add some information to the prognosis of conservative treatment. Walton[4] studied 312 patients with subarachnoid hemorrhage and found an initial mortality of 45% and an 11% mortality due to recurrence of the bleeding. Over half of the late recurrences occurred in the first six months after the original episode, so mortality in those patients surviving the first six months was less than 5%. Rowley, Sullivan, and Tureen[14] had similar results in a smaller group.

A group of 40 patients with intracranial aneurysms diagnosed by angiography or at postmortem examination who received no surgical treatment are reported by af Björkesten and Troupp.[10] Reasons given for nonsurgical care were that some were treated at a time when surgical attack of intracranial aneurysms was not performed, some refused surgery, and the rest were not considered good surgical candidates. Of these patients, 22 died, 18 within the first six months; thus, they report a 10% mortality rate in patients with proved intracranial aneurysms who survive six months after the initial episode.

PRESENT SERIES

This series includes 40 patients with angiographically proved intracranial aneurysms treated at the San Francisco Veterans Administration Hospital from 1946 to 1956.

Because of the transient population treated in this type of hospital, the follow-up study has been difficult and not entirely successful. However, the data gathered do shed some light on the long-term prognosis of conservatively treated intracranial aneurysms. Of these 40 patients, 17 are known to be dead, 14 are still living, and 9 have disappeared from the study group; 22 were treated surgically, and the remaining 18 patients were either treated conservatively or died before surgery could be performed.

RESULTS

Table 1 shows the duration of survival after the initial hemorrhage of those known to have died. As can be seen from the table, there were 8 deaths in the operated group and 9 deaths in the nonoperated group, with 13 of the 17 deaths occurring in the critical period following onset of symptoms. Of the deaths occurring a year or more after the original disease, the 2 deaths in the surgically treated group were as a result of their aneurysm. Death occurred during craniotomy for treatment of an aneurysm of an anterior cerebral artery in 1 patient with a two-year history of progressive deterioration before hospitalization; recurrent bleeding from an anterior cerebral aneurysm one year and five months after carotid ligation caused a second death.

In the conservatively treated group, 1 died two years after subarachnoid hemorrhage from a myocardial infarction and the other died of multiple cerebral vascular accidents eight years after the initial episode of subarachnoid hemorrhage. Thus, of the original 40 cases of angiographically diagnosed intracranial aneurysms, 13 (33%) died within the first three months after onset and another 2 (5%) died subsequently as a result of this disease. The other 2 known dead cannot be considered to have died of their aneurysm although this may have contributed in a greater or lesser amount.

Survival times of the 14 patients who are still alive are shown in Table 2. Again it can be seen that the surgically and the nonsurgically treated groups are about equal, each having 6 cases with survival time of one to eleven years. The two other cases of known survivors must be mentional separately; both had angiographically proved aneurysms and neurosurgery, but in neither case was the aneurysm attacked; 1 patient who has survived one and a half years after a subarachnoid hemorrhage underwent a Torkildsen procedure to relieve hydrocephalus and the other who has survived almost five years since initial bleeding prudently refused subsequent surgery after he

had the wrong internal carotid artery ligated. Both of these cases should be included in the nonoperated group for purposes of survival studies although certainly in the first instance and possibly in the second the surgery has improved the length of survival.

Follow-up data are lacking for 9 patients in the present study who failed to return their questionnaires and have thus far eluded tracing attempts; of these, 6 were treated surgically and 3 were handled conservatively. There is no honest way to estimate the survival or prognosis of this group; however, it can be said that all were able to be discharged from the hospital after treatment.

Including the 2 patients whose surgery did not directly affect the aneurysm, we have 20 cases of nonoperated aneurysms to study. Death occurred within two months of the first subarachnoid hemorrhage in 7 instances; 2 patients survived the bleeding episode only to succumb to another disease process; 8 are known living from seven months to eleven years after their original hemorrhage; and 3 are unreported.

A total of 10 cases survived their ruptured intracranial aneurysm; of course, we are unable to be certain that some of this group will not eventually have a fatal recurrence. However, from the statistical studies of Walton[4] who found a 5% and of af Björkesten and Troupp[10] who found a 10% fatal recurrence rate after six months of survival, we would not expect more than 1 or 2 of the present series to be so involved.

From table 2, it can be seen that the time of survival in this conservatively treated group is fairly high. The range is from seven months to eleven years, and the average length of survival of the entire group is six years and one month. Only 1 patient in this group of 10 had a recurrence. This occurred two and one-half years after his original episode, and he has now survived eight and one-half years without a recurrence of bleeding.

TABLE 2
TIME OF SURVIVAL AFTER INITIAL HEMORRHAGE

	Surgically treated cases	*Conservatively treated cases*
0 to 1 year		1
1 to 2 years	1	1*
2 to 3 "	2	
4 to 5 "	1	1*
5 to 6 "	1	
7 to 8 "		1
8 to 9 "		2
9 to 10 "		1
10 to 11 "	1	
11 to 12 "		1

*See text for discussion of these two cases which had surgery but should be considered as conservatively treated aneurysms.

COMMENT

While the number of cases included in this series is far too small to be of real prognostic significance, the results do offer some indications in a previously uncharted domain. Each patient included in this series had a subarachnoid hemorrhage, the etiology of which was proved by cerebral angiography to be a ruptured intracranial aneurysm. They were then treated conservatively, either at the discretion of the hospital staff or at the patient's own direction. The 10 patients who survived the dangerous first two months are still alive an average of six years and one month after their original attack or have succumbed to some other process. Thus, this study indicates a rather favorable prognosis for longevity in those cases surviving the early danger period. On the basis of these data and those of the other recent references cited, we do not recognize the high late fatal recurrence rate accepted from older studies of subarachnoid hemorrhage. In fact, it would appear that the surgical mortality rate is higher than the fatal recurrence rate in cases seen six months or more after their bleeding episode.

DISCUSSION

The number of reported cases of conservatively treated ruptured intracranial aneurysms is both small and misleading. In the past ten years, angiographic proof of the existence of an aneurysm as the cause of subarachnoid bleeding has led directly to the question of which surgical procedure should be carried out and when this should be done. By and large, the only cases treated conservatively were

those who died before surgery could be performed or who had some definite contraindication to surgery. The first group with an overwhelming original hemorrhage remains a distinct but not too hopeful challenge to all concerned. The second group has remained small at better neurosurgical centers. Thus, we have a definite lack of adequately documented cases of conservatively treated bleeding aneurysms in the literature.

The statistics usually referred to in predicting the outcome of conservatively treated intracranial aneurysms are those of subarachnoid hemorrhage. This is a symptom complex, not a specific disease entity, and the prognosis varies with the etiologic factor. Odom, Bloor, Golden, and Woodhall[11] reported on the outcome of a large series of subarachnoid hemorrhage cases divided into their specific etiologies and found striking differences in mortality for the different disease entities. The mortality range was from 33% for bleeding A-V malformations to 100% for spontaneous intracerebral hematoma. If one excludes trauma, probably over one-half of the cases of subarachnoid hemorrhage are due to rupture of an intracranial aneurysm. Even so, it is hardly accurate to consider the long-term prognosis of these two as equivalent. Many of the other causes of subarachnoid hemorrhage are chronic degenerative processes with an ultimately fatal outcome; for instance, bleeding into a tumor, blood dyscrasias, intracerebral hemorrhage, and heavy metal toxicity are all causes of subarachnoid bleeding with a generally poor prognosis. Thus, we find that the statistics used at present to predict the outcome of conservatively treated intracranial aneurysms are weighted with prognostically unfavorable cases which are not aneurysms. Perhaps this explains the discrepancy between the dismal long-term prognosis usually quoted and the more favorable findings in our series and that of af Björkesten and Troupp.[10] Certainly it points out the need for larger and better follow-up studies on conservatively treated cases of intracranial aneurysms.

Another statistical fallacy can now be seen. Since the work of Mount[5] in 1951, most neurosurgeons[2,3,9,11,13] have compared the accepted high mortality statistics of subarachnoid hemorrhage usually given as 60% or greater with the 14% surgical mortality of intracranial aneurysms and from this concluded that almost all aneurysms deserve surgical treatment. We have seen that the 2 groups cannot be honestly compared. There is another discrepancy beyond this fact. Odom[11] showed that one-half of all deaths due to bleeding aneurysm occur within two weeks of the initial hemorrhage and that two-thirds of the deaths occur in the first three weeks. Most neurosurgical attacks on aneurysm are delayed two weeks or more after the initial hemorrhage, so this very sizable number of fatalities present in conservatively treated series does not appear in the surgically treated group. Thus, it becomes apparent that patients who survive long enough to undergo surgery have a far better prognosis than the group as a whole and brings into doubt the statistics proving that all bleeding aneurysms deserve surgical therapy.

CONCLUSION

From this admittedly small study, the following conclusions can be drawn:

1. Subarachnoid hemorrhage and bleeding intracranial aneurysm are not the same entity and have different prognoses.

2. There is need for more study of the long-term prognosis of conservatively treated ruptured intracranial aneurysms.

3. Conservatively treated aneurysms that survive the dangerous early period have a relatively favorable prognosis.

Our findings indicate that the following considerations can be raised:

1. Excluding those patients who terminate fatally in the early danger period, conservatively treated and surgically treated aneurysms have nearly the same prognosis.

2. Some cases of bleeding intracranial aneurysm are best treated conservatively.

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■ Epilepsy has been variously classed and distinguished by different authors. Galen considers the disease as of three kinds; the first being a direct affection of the head; the second primarily of the stomach, and secondarily of the head; and the third that in which the affection begins in some distant part and ascends to the brain.

Sauvages divides epilepsy generally into the perfect and the imperfect, which he subdivides into many species, according to the causes of each. Thus he describes the *plethoric* epilepsy, the *cachectic*, the *stomachic*, &c.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824

Peripheral nerve–spinal cord anastomosis for experimental cord transection

C. C. Turbes, D.V.M., and L. W. Freeman, M.D.

A NUMBER OF INVESTIGATORS have studied the ingrowth of peripheral nerves into the central nervous system. Clark[1] inserted the distal end of peripheral nerves into the brains of rabbits to observe whether axons of the central neural cells would grow into the inserted peripheral nerves. Although he found they did not, his photographs show vigorous ingrowth of the peripheral nerve into the brain.

Clemente, Chambers, and Windle[2–4] inserted cranial nerves into the brains of cats to evaluate the scar-inhibiting action of certain agents and the scarring response to the insertion of peripheral nerves. Jacoby, Turbes, and Freeman[5] inserted from 1 to 4 intercostal nerves into the spinal cord around transecting lesions to study changes in reflex activity of the isolated distal segment of the cord.

The present study is an initial report on changes in reflex activity of the distal cord segment in dogs in which 1 intercostal nerve was used to bridge a complete lesion.

EXPERIMENTAL METHOD

Surgery was done, under strictly sterile conditions, on 30 healthy adult female dogs weighing approximately 25 lb. each.

Complete lesions of the spinal cord were made by removing 1 cm. of the spinal cord and its ensheathing meninges during open laminectomy at the level of the eighth thoracic vertebra (Fig. 1A). One to two months after this operation, an intercostal nerve–spinal cord anastomosis was made (Fig. 1B). This was carried out by extending the old surgical wound through the ninth vertebral spine and lamina until the proximal portion of the distal segment of the spinal cord was exposed to about 2 cm. below the complete lesion scar. The seventh intercostal nerve was dissected free from its interspace and divided where the lateral branch leaves the anterior division.

A fine silk suture with swaged-on needle was attached to the distal end of the nerve. A curved Péan forceps was passed through the surgical opening laterally beneath the longissimus dorsi and longissimus costarum muscles to form a tunnel for the nerve. The suture and attached nerve were grasped and pulled into the laminectomy opening. The dura mater of the distal stump was opened in the midline and the edges retracted by sutures.

An avascular area at the dorsal aspect of the exposed cord segment was chosen for insertion of the distal nerve end. The pia mater was incised sharply with a dagger point, and the needle was inserted through the opening, into the spinal cord to half its depth, then passed laterally to the right and out of the cord. Traction was applied to the suture, and a fine forceps was used to guide the nerve well into the spinal cord. The nerve was anchored by using the suture to close the dural opening.

Of the 30 animals, 25 developed reflex standing and walking* after the nerve insertion. These dogs were chosen for surgical section of the nerve, which was cut just above

*The terms "reflex standing" and "reflex walking" have been used as expedients, since many of the observers in our laboratories have insisted that the activities could be none other than voluntary. Since this laboratory considers standing and walking as coordinated reflex patterns, resolution of the terms will require further experimentation.

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its insertion into the cord in 3 animals and just distal to its emergence from the intervertebral foramen in 2 others (Fig. 1C and D). The animals were sacrificed after two or three months.

At the end of each experiment, the cord segment containing the lesion and the inserted nerve was dissected free. The specimen was then divided to facilitate sectioning (Fig. 1). Each segment was fixed in neutral 10% formalin, embedded in paraffin, and sectioned serially. A detailed histologic study was made of the lesion and the area of peripheral nerve insertion, using special nerve fiber stains – modified Cajal silver, Bodian, and Bielschowsky. Weigert and Weil's methods were used in myelin staining, and Mallory's triple stain was used for collagen.

RESULTS

Generally, 25 of the 30 dogs reacted as follows: Changes in the reflex patterns began to appear within ten days to two weeks after insertion of the nerve. Characteristic was placement of the rear footpads on the floor in a squatting manner, rather than dragging the rear extremities with drop feet, as previously. Later reflex standing and incoordinated steps were observed. Gradually, the animals became capable of standing for longer periods and of taking a greater number of reflex steps. During or following defecation and urination, the animals demonstrated fairly coordinated reflex walking.

Manual assistance was needed for bladder evacuation before insertion of the nerve into the cord. From the time reflex standing and walking appeared, automatic emptying of the bladder and rectum continued unaided.

Spontaneous clonic-like movements occurred with increasing frequency after periods of reflex standing and walking. These movements involved primarily the distal joints of the rear limbs, exclusive of the digits.

Animals capable of reflex standing and walking did not acquire decubitus sores, "fixation"

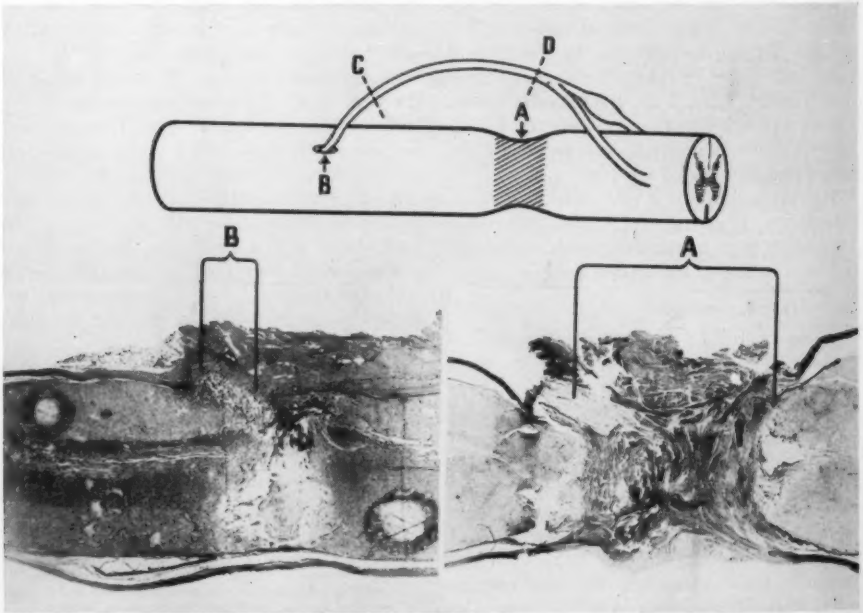

FIG. 1. Diagram of preparation and photomicrograph of spinal cord sections. [A] Scar of complete lesion. [B] Cross section of inserted nerve beneath the scar on the dorsum of the cord. [C] Surgical section of the inserted nerve just above the cord. [D] Surgical section of the inserted nerve at the intervertebral foramen.

of the joints of the extremities, or other complications observed in most dogs with complete experimental spinal cord lesions.

Serious bladder and kidney complications frequently seen in paraplegic dogs were few, only 11 animals having bladder infections which needed treatment.

Of the 30 animals, 4 did not develop reflex walking and standing but did automatically evacuate bladder and rectum. Weight loss, decubitus sores, and genitourinary problems did not occur.

The 5 dogs in which the inserted nerve was resected reacted similarly whether the section was near the cord or the intervertebral foramen. All 5 dogs lost ability of reflex standing and walking within two to three days, this deficit remaining until the end of the experiment. Bladder and rectal function remained automatic and weight fairly constant.

Metabolic status of the 30 animals changed considerably within four days to one week after peripheral nerve–cord anastomosis, though no specific metabolic tests were made. All animals lost weight after the initial lesion was made. Of the animals with good reflex standing and walking, 2 did not regain their initial weight, 1 losing 3, the other 7 lb., but both appeared healthy throughout the experiment. In 8 animals which gained excessive weight, dietary measures were instituted. Two-thirds of the animals returned to and maintained their initial weight, none gaining more than 3 lb. during the experimental period.

PATHOLOGIC FINDINGS

Complete lesion area. Upon gross examination of the specimens, a dense connective tissue scar could be followed from the skin wound down to the laminectomy opening. Scar tissue adhered to the ends of the proximal and distal spinal cord segments, to the stumps of the neural arches, and to the posterior longitudinal ligament. Between the ends of the spinal cord segments, the scar became a dense, poorly vascular mass adhering to the adjacent meninges. The subarachnoid space was completely blocked. The cerebrospinal fluid around the distal end of the proximal segment was plentiful and colorless; around the distal spinal cord segment, considerably less in volume, being difficult to collect and observe.

Histologically, the scar at the site of transection was a dense mass of collagenous connective tissue. Nerve fibers frequently extended into the scar at the dural adhesion area but could never be traced for any distance. Strands of glial and connective tissue containing intact-appearing axons and blood vessels connected the distal end of the proximal stump and the scar. Fewer strands were observed between the distal cord segment and the scar. In neither case could nerve fibers be traced through the scar.

Area of peripheral nerve insertion. The major scar mass was mainly limited to the point of insertion over the dorsum of the spinal cord and extended laterally to enshroud the anchoring suture.

Histologically, the scar was predominantly collagenous connective tissue, most dense around the anchoring suture, less dense and more vascular near the nerve. The nerve could be followed from the opening in the pia into the surgical wound cavity within the spinal cord. Fascicles of tissue containing many nerve fibers, Schwann-like cells, and their processes could be followed from the distal end of the nerve to the wound edges and into the substance of the spinal cord. Most regenerating nerve fibers turned into the distal isolated segment of the spinal cord, following closely the intact central axons and blood vessels.

Fewer regenerating peripheral nerve axons were observed growing into the distal segment between the lesion scar and the inserted peripheral nerve. In this segment, only a few axons were intact. Elements consisted mainly of fragments of degenerating axons with associated phagocytes and an increased number of glial elements. Fine nonargyrophilic fibers extended into this portion of the cord, becoming most dense near the wound edges. They did not stain with collagen or myelin preparations and were more closely associated with glial cells. Relatively few such fibers were found in the proximal end of the distal segment (Fig. 2).

Cells resembling those of the sheath of Schwann were most dense around the peripheral nerve stump. Many fine nerve fibers traversed the mass of Schwann-like cells, extend-

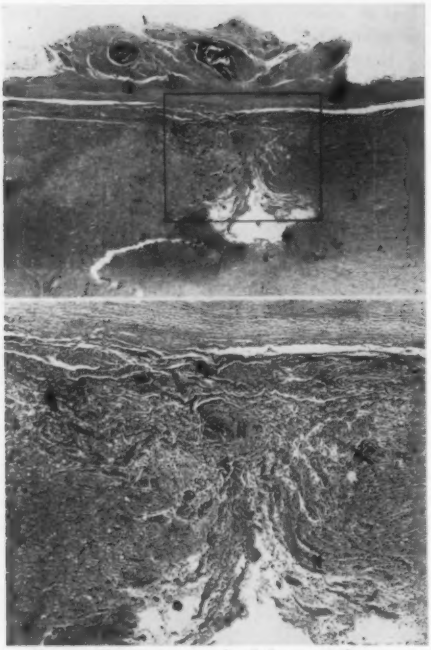

FIG. 2. Photomicrograph of the area of nerve insertion. *Top:* The scar on the dorsal aspect of the cord. Within the square are shown the inserted nerve and ingrowing bundles of peripheral nerve. Made with Bielschowsky's silver stain and magnified 60 times. *Bottom:* The area within the square magnified 200 times; *N* is inserted intercostal nerve and nerve bundles growing into the isolated distal segment of the cord.

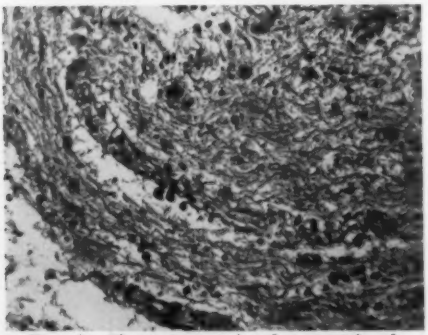

FIG. 3. Photomicrograph of a peripheral nerve bundle growing into the cord, made with Bielschowsky's silver stain and magnified 400 times.

ing into the substance of the spinal cord (Fig. 3). The regenerating fibers of the peripheral nerve within the cord were closely associated with persistent intact spinal cord axons and reacted positively to myelin stains. Generally, ingrowing peripheral nerves and associated Schwann-like cells extended beyond the microscopic sections.

Histologic analysis of the 5 dogs which did not develop reflex standing and walking helps clarify the basis for their nonperformance. In 2 of the animals, the nerve was placed into the cord just adjacent to the complete lesion scar. Very few axons grew into the isolated distal segment; most nerve fibers were in the loose scar tissue of the complete lesion. In 1 dog, the distal end of the nerve was pulled completely through the cord substance, and the nerve fibers were growing into the scar and adjacent meninges.

The remaining dog showed very little nerve ingrowth in spite of the fact that the nerve seemed properly inserted into the cord. Examination of the nerve distal to its insertion showed few fibers. Histologic analysis of the origin of this nerve indicated that the complete lesion was too close to the cells contributing to the inserted nerve. Extensive death of anterior horn cells resulted, leaving posterior root components as the major nerve constituents.

Following sectioning of the peripheral nerve, assessment of the fiber degeneration was difficult. Much of the regenerated peripheral nerve fiber was apparently removed by phagocytes during the degenerative changes consequent to cutting of the nerve.

DISCUSSION

In this laboratory, in a large number of adult dogs, surgical transection of the spinal cord has rarely been followed by development of reflex standing and walking.[6]

Shurrager (see Windle[7]) described the development of spinal standing and walking in cats and dogs with chronic spinal disorders after the conditioning procedures. Shurrager and Dykman[8] stated that if the spinal cord was transected in the first few days of life in kittens and puppies, a fairly well coordinated walk developed without training or conditioning.

But if the animals had begun to walk when the cord was transected, systematic stimulation and training were necessary to establish a kind of coordinated walking pattern.

In this experiment, insertion of an intercostal nerve from the proximal spinal cord into the isolated distal segment of the cord resulted in walking and standing without conditioning, stimulative, or training procedures. Changes in mass, spatial organization, and constituents of the scar associated with the distal segment of the cord resulted from the insertion.

The significance of these changes and their relation to the mechanisms underlying the reflex phenomena are not known. Scarff and Pool[9] concluded that the scar was an important factor in massive spasms in human paraplegia and reported alteration of spasms after surgical removal of the scar and sectioning of the distal posterior columns.

Initial evidence of the present study indicates that nerve fibers are important in development and maintenance of reflex standing and walking, since surgical section of the inserted nerve resulted in loss of these activities. Jacoby, Turbes, and Freeman[5] showed that reflex walking and standing could be reestablished by insertion of another peripheral nerve into the distal segment of the cord following section of the first nerve. Connective tissue, vascular, and glial constituents of the scar must also be considered as factors in further analyses.

Changes in visceromotor function of the distal isolated segment of the cord are difficult to evaluate. Apparently, somatic reflexes were closely coordinated with visceromotor activity. Frequently, bladder and rectal evacuation were observed during reflex walking, and reflex walking appeared more coordinated at such times.

SUMMARY

1] Complete lesions were made in the spinal cord of dogs by removing a portion of the spinal cord and its ensheathing meninges.

2] One to two months later, the distal stump of an intercostal nerve having its origin above the lesion was inserted into the isolated distal segment of the spinal cord.

3] Within ten days to two weeks after insertion of the nerve, the dogs attempted to stand and walk. In the following months, longer periods of standing and more coordinated walking developed.

4] Five animals which had developed reflex walking and standing lost these functions after surgical section of the inserted nerve.

5] Histologically, nerve fibers and Schwann-like cells extended from the distal end of the inserted peripheral nerve into the isolated distal segment of the spinal cord.

The authors wish to acknowledge the able and devoted assistance of Mildred Redford in the conduct of these experiments. The photographs, photomicrographs, and other illustrations were made possible through the generous cooperation of James F. Glore and his assistant, Paris Johnson.

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Clinical and pathologic findings in vertebral artery thrombosis

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THIS paper is presented to define more clearly the clinical syndrome and pathologic findings in patients with thrombosis of a single vertebral artery.

In 1947, Pratt-Thomas and Berger[1] presented 3 patients in whom thrombosis of the basilar artery or a vertebral and/or cerebellar artery ensued after chiropractic manipulation of the neck. Biemond[2] described a patient with right-sided hemiplegia including paralysis of the lower part of the face; dysarthria; dysphagia; left-sided hemiparesis; bilateral, positive Babinski signs; and paralysis of the seventh, ninth, tenth, and twelfth cranial nerves. Postmortem examination revealed the left vertebral artery to be thrombosed, with extension of the thrombus into the basilar artery. Ford[3] described a patient who had syncope, vertigo, and visual disturbances that were thought to result from intermittent obstruction of the vertebral arteries due to an almost complete lack of the odontoid process and excessive mobility of the second cervical vertebra. Van der Zwan[4] reported 2 cases of vertebral artery thrombosis, as demonstrated by basilar artery filling on carotid angiograms. Ford and Clarke[5] described 2 patients in whom vertigo, nausea, semistupor, loss of vision in 1 eye, and noises in 1 ear occurred after chiropractic manipulation. Both had tendencies to fall toward 1 side and complained of clumsiness. Postmortem examination of 1 patient revealed thrombosis of the basilar, left posterior cerebral, and left posterior inferior cerebellar arteries. In 1956, Hutchinson and Yates[6] performed autopsies in 48 patients with various cerebrovascular lesions and found atheromatous changes of the cervical portion of the vertebral artery in 19. Of the 19 patients, 4 had cerebral hemisphere as well as cerebellar infarctions and, in 3 of the 4 patients, the cerebellar changes were bilateral. Occlusion was caused by a thrombus in 1 patient and atheromatous plaques in the other 3. Atheromatous changes were extensive in many of the cerebral vessels, with what appeared to be insufficiency of these vessels. In 1957, Hutchinson and Yates[7] reviewed post mortem the cerebral vascular trees, including the whole length of the vertebral and carotid arteries, of 83 patients with cerebrovascular disease. The carotid and/or vertebral arteries were occluded by extensive atheromatous changes in many instances. A clinical syndrome and pattern of infarction was reported in those patients who had had vertebral artery disease. Vertebral artery occlusion without carotid artery occlusion was found in 6 patients, and, of these, 2 had actual thrombus in the vertebral artery. Occlusion in the other 4 was caused by atheromatous plaques. Krayenbuhl and Yasargil[8] described a hypertensive patient with left vertebral artery thrombosis who presented with sudden headache, inability to swallow, stiff neck, dysarthria, nystagmus, weakness of the right upper and lower extremities, hypotonia, and left peripheral facial paralysis.

We have collected clinical and postmortem data on 6 patients with thrombotic occlusion of a single vertebral artery in whom the opposite vertebral artery and the basilar and carotid arteries were patent and showed no significant impingement upon the lumen by atheromatous changes. We felt that such a selection would allow a more critical evaluation of

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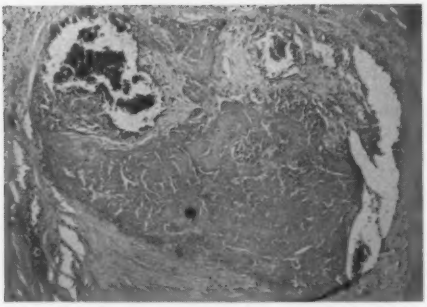
the effects of vertebral artery thrombosis or insufficiency.

PATIENT MATERIAL

Average age of patients at onset of symptoms was 63.5 years. The youngest patient was 48 and the oldest was 80 years old. Of the 6 patients, 4 were men. All patients had associated systemic disease – 1, diabetes; 2, hypertension; and 3, both. Of the hypertensive patients, 1 had had hypertension for forty years, the blood pressure being approximately 240/140. The other patient had a blood pressure reading of 170/100 and had had angina for five years, with a coronary occlusion eleven months before admission. The course of disease in each case was marked by central nervous system signs and symptoms preceding the final vertebral artery occlusion. After the initial central nervous system manifestation, every patient but 1 markedly improved before onset of the terminal episode. Of the 6 patients studied, 3 have been selected for detailed report.

Case 1, a 48-year-old white man, was admitted for the first time to the University Hospital complaining of vomiting, weakness, vertigo, and sweating. Diabetes of seventeen years' duration recently had been controlled by daily administration of 25 units of lente insulin. The urine usually was negative at this dosage, but, the day before admission, he reported that it was positive. The blood pressure had been elevated since the age of 16 years. Six weeks before admission, an intense, bilateral, periorbital headache appeared but subsided after two hours. Numbness of the right side of the neck, right arm and leg, and trunk ensued. The patient complained that swallowing was impossible at this time and that breathing could be done only while sitting up. The right side of the face drooped somewhat, but the right arm and leg were not weak. These symptoms gradually disappeared within eleven days after the original episode. On the day of admission, the patient arose from bed and complained that the room was spinning about him. Twelve to twenty minutes after returning to bed, he became nauseated and vomited. During the day, he vomited four more times. A buzzing sound was heard in the left ear, and the patient was generally weak. On admission, the pulse was 100; blood pressure, 190/100; respiration, 20; and temperature, 99° F. The patient was well developed and well nourished and appeared drowsy but oriented. The physical examination was essentially negative. Neurologic examination revealed the patient to be dysarthric. Deglutition was unsatisfactory for solids and liquids. Also noted were paresis of the left internal rectus muscle and ophthalmoplegia of the right eye, involving gaze in all directions except upward and medially. The remainder of the neurologic examination, including tests of gait, coordination, motor power, reflexes, sensation, and cranial nerves, was normal. The day after admission, nausea and vomiting recurred. Two days later, drowsiness increased and bilateral horizontal nystagmus developed. Three days after admission, weakness of the right levator palpebra appeared and the right eye tended to deviate medially. Sensation to pinprick and light touch on the right side of the face was decreased, and some right-sided facial weakness, manifested by drooping of the corner of the mouth, was apparent. A right Babinski sign was elicited. On the day before death, clonic movements of the upper extremities, bilaterally, lasted approximately twenty minutes. Laboratory studies of the blood, urine, electrolytes, and spinal fluid were negative, except that fasting blood sugar was 143 mg. per cent and urinary sugar was 1 to 2+, with no acetone. A chest roentgenogram was normal.

Postmortem examination revealed focal, chronic, bilateral pyelonephritis; fatty metamorphosis of the liver; and marked coronary atherosclerosis with subintimal infiltration. Upon examination of the brain and arteries, a well-organized thrombus showing early signs of recanalization in the left vertebral artery was found (Fig. 1). Layers of platelets, red cells, fibrin, and leukocytes, as well as endothelial proliferation, were noted within the thrombus. The walls of the vertebral arteries showed marked atheromatous changes, with subendothelial thickening and cholesterol and fatty deposits. A slight amount of hemorrhage was present within the wall of the media at 1 point in the left vertebral artery but did not involve the adventitia. The elastica appeared intact except in the area of the thrombus, where continuity of the elastica was not visible. Some calcification occurred within the walls of the vessels. Sections of the brain stem showed marked encephalomalacia on the left side at the level of the upper pole of the inferior olive and restiform body, extending up to a level parallel with the first appearance of the brachium pontis. In these areas, the abnormal changes were seen in the ventral lateral aspect of the pons on the left. There was loss of tinctorial properties and neuronal chromatolysis in the intralaminar nuclei, with destruction of pontine fibers. In the subependymal region in the floor of the fourth ventricle, small, oval-to-round hemorrhages were seen bilaterally, and an area of encephalomalacia 2 mm. in diameter was noted 1 to 2 mm. from the ependyma of the fourth ventricle, 2 mm. to the left of the midline. The area of encephalomalacia included the left side of the restiform body, vestibular nuclei (Fig. 2), basis pontis and region of the corticospinal fibers, spinothalamic fibers, and nucleus ambiguous. Except for thrombosis of the vertebral artery, examination of the other vessels of the Circle of Willis showed no significant impingement upon the lumen.



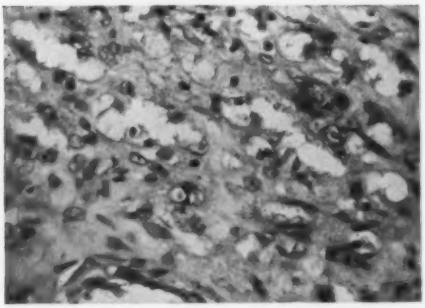
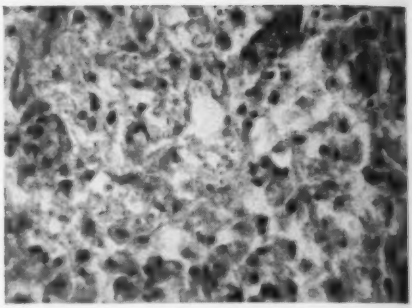


Fig. 1. Left vertebral artery and thrombus (hematoxylin-eosin stain). Magnification × 90 *(top)* and × 500 *(bottom)*



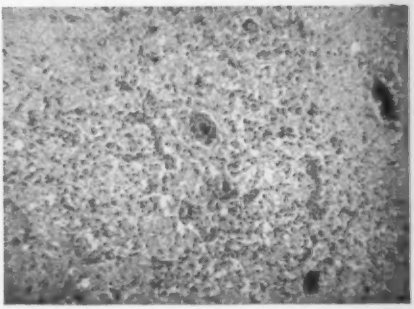


Fig. 2. Encephalomalacia surrounding and extending to involve vestibular nuclei on left (hematoxylin-eosin stain). Magnification × 70 *(top)* and × 500 *(bottom)*

Clinicopathologic correlation is as follows: The vertigo, nausea, vomiting, and nystagmus probably related to the involvement of the vestibular nuclei and their proximal fibers. Hypesthesia and hypalgesia of the right side of the body and face were caused by involvement of the spinothalamic tract and, possibly, the medial lemniscus on the left side, with apparent involvement of the lemniscus of the fifth nerve on the left. This may have been due to ischemia rather than encephalomalacia, since the latter was not seen in the sections. Involvement of the spinothalamic tract was observed, however, and accounted for the numbness of the right side of the body. The right facial weakness also appeared to indicate an involvement of supranuclear fibers on the left side. A right-sided Babinski sign related to the involvement of the basis pontis and left corticospinal fibers. Impaired swallowing and dysarthria resulted from pathologic changes in the nucleus ambiguous. The buzzing sound in the left ear was due to involvement of the left internal auditory artery. The difficulty in movement of the right eye, internal deviation of the right eye, and weakness of the levator palpebra on the right could not be explained by the pathologic changes but may have been caused by ischemia occurring higher up than where the histologic abnormality was seen. The spinal tract of the fifth nerve and nucleus seem to have been spared functionally on the left side, and Horner's syndrome was not apparent.

Case 2, a 59-year-old white man, was admitted to the University Hospital for the first time. The patient had been in good health before onset of symptoms five days previously, when he suddenly became ill, with nausea, vomiting, severe objective vertigo, and pain and loss of hearing in the right ear. He was alone at the time and was not sure if he had remained conscious. Disorientation ensued, and the patient was unable to reach the telephone to call for help. The next day, he was somewhat better but noted numbness of the left arm and leg and peculiar sounds in the right ear accompanied by vertigo. The patient's wife stated that he was difficult to understand, though he seemed able to understand her. On the day of admission, the patient had another attack of pain and sudden loss of hearing in the right ear, difficulty in swallowing, labored respiration, objective vertigo, nausea, vomiting, numbness of the left leg, and dysarthria. Diabetes of seven years' duration

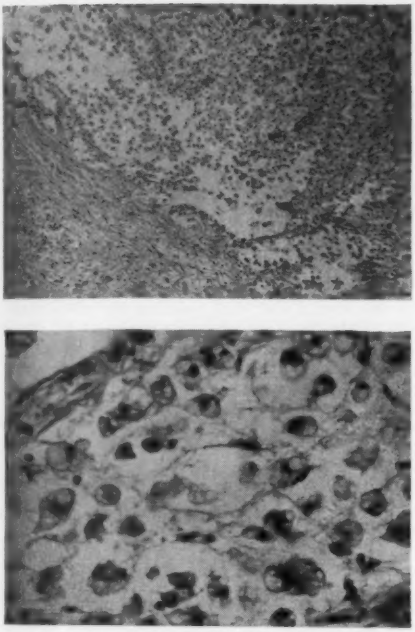


Fig. 3. Cerebellar folia and lesion on right side (hematoxylin-eosin stain). Magnification × 90 *(top)* and × 500 *(bottom)*.

had been controlled by diet alone. Physical examination revealed the temperature to be 101.5° F.; pulse, 48; respiration, Cheyne-Stokes; and blood pressure, 100/60, later rising to 144/70. Positive findings upon neurologic examination included nystagmus on left lateral gaze, absent gag reflex, and poor palatal motion on both sides. Proprioception and pinprick sensation on the left side of the body and muscle strength in the left arm and leg were decreased. After treatment with Heparin, respirations appeared to become regular. Two days after admission, paralysis of the left arm and leg became complete. Laboratory studies revealed a fasting blood sugar of 179 mg. per cent. Urine was negative for sugar. Nonprotein nitrogen was 50 mg. per cent. On the third hospital day, the fasting blood sugar was 32 mg. per cent but was corrected in eighteen hours to 114 mg. per cent. Serologic examination was negative. The patient died on the fifth hospital day.

Pathologic changes included a small area of necrosis and suppuration in the lower lobe of the right lung, occlusion of the left subclavian vein, and intercapillary glomerulosclerosis. Examination of the brain and arteries revealed a thrombus in the right vertebral artery close to the bifurcation of but not extending into the basilar artery. The thrombus was well organized but showed no signs of recanalization. Sections of the cerebellum showed encephalomalacia of the right semilunar lobule, including the superior and especially the inferior lobules. Changes were seen within the granular layer of several folia as well as the medullary and cortical layers. Encephalomalacia appeared as small, circumscribed, and irregular lesions. In some regions, encephalomalacia was so extensive that the normal morphology of the folia was disrupted completely. Microcystic changes were observed in the semilunar lobule on the right, with many gitter cells, as well as ischemic cell changes throughout the Purkinje layer (Fig. 3). Sections of the brain stem revealed ischemic cell changes in neurons at the level of the restiform body on the right side affecting the vestibular and cochlear nuclei as well as the nucleus ambiguous. Ischemic cell changes were also present in the region of the basis pontis on the right.

Clinicopathologic correlations is as follows: A thrombus in the vertebral artery on the right side produced symptoms similar to those in case 1 and conformed to the general region of the blood supply of the vertebral artery. Ischemic cell changes in the vestibular nuclei probably related to vertigo, nausea, and vomiting. Weakness of the left side was caused by alterations in the right pons. Loss of hearing in the right ear was due to involvement of the right internal auditory artery. Cellular ischemia may induce the clinical syndrome described before inducing gross or microscopic alterations in cell structure.

Case 3, a 70-year-old white woman, was admitted for the first time to the University Hospital with chief complaints of progressive drowsiness, inability to read, and weakness of one day's duration. She had been hypertensive for forty years. She had headache, dysphagia, tinnitus, deafness on the right side, vertigo, and a tendency to fall toward the right when walking. The headaches, vertigo, and tinnitus became progressively worse. These symptoms appeared to come and go throughout the illness but, just before admission, occurred every day. The patient stated that she was losing her memory and that her vision had been blurred for four months. On the day of admission, she suddenly complained of inability to read and extreme difficulty in swallowing. She lost the sense of awareness of surroundings with her eyes closed and was unresponsive for minutes at a time. Blood pressure was 240/140; temperature, 100.4° F.; pulse, 68; and respiration, 20. The patient was dysarthric and dysphagic and appeared comatose but responded to painful stimuli. The pupils were constricted bilaterally but were round, regular, and equal. Reaction to light was sluggish on both sides. There was right peripheral facial weakness, with spastic paralysis of the left arm and leg. The right arm and leg were weak. Bilateral Babinski signs and hyperactive deep tendon reflexes were elicited. All laboratory studies were essentially negative. Death occurred on the second day of hospitalization.

Autopsy was noncontributory. Examination of the brain and Circle of Willis revealed a thrombus within the lumen of the right vertebral artery. The clot was well organized but showed little recanalization. The elastica was intact, and the media was slightly fibrosed. Several areas were calcified medial to the elastica. The left vertebral artery was approximately one-half the size of the right, with some fibrotic changes in the media and calcification and deposition of fatty materials and cholesterol. Section at the level of the eighth nerve showed 2 small hemorrhages in the region of the right ventral cochlear nucleus and vestibular nuclei and restiform body, extending into the fibers of the facial nerve. All of these changes were on the right side. Some caudal extension involved the region of the olivocerebellar fibers and nucleus ambiguous on the right. However, examination of the basis pontis at the level of the eighth nerve fibers showed several areas at the midline that extended laterally to both sides of the pons to the medial aspect of the corticospinal fibers. Staining properties in these regions were poor, and loss of nerve cells was evident within the intralaminar nuclear groups. The remaining brain sections, which included the cerebellum, showed no significant abnormalities.

Correlation of clinical and pathologic findings is as follows: Tinnitus and deafness on the right side were caused by involvement of the right internal auditory artery. The vertigo and tendency to fall to the right related to lesions in the vestibular nucleus, and the dysphagia and dysarthria were due to extension of encephalomalacia to the nucleus ambiguous. The right peripheral facial palsy related to involvement of the fibers of the facial nerve close to the point of exit from the brain stem. The left spastic paralysis and weakness on the right side were due to the midline lesion in the pons, which extended on both sides toward the corticospinal fibers. Blurring of vision did not directly result from the histologic changes, and the impairment in memory related to a more diffuse deficiency.

Case 4 had similar symptoms and signs, including transient, left-sided numbness and weakness of one year's duration. This cleared completely until five days before admission, when numbness of the left arm and leg suddenly reappeared, followed by weakness of the left arm and leg and left side of the face. Other symptoms were dysarthria and headache. The patient became comatose on the ninth day and died on the tenth day. Histologic examination revealed a thrombus in the right vertebral artery. An area of encephalomalacia measured 6 cm. from side to side and primarily affected the posterior and posterolateral aspects of the right inferior semilunar lobule. A small lesion occurred medial to this and extended to the edge of the vermis. Another area of encephalomalacia was found in the region of the basis pontis, extending from the midline to the lateral edge of the pons on the right and to a point approximately two-thirds of the way up toward the tegmentum. The left vertebral artery was approximately one-fourth the diameter of the right. The right pontine lesion was responsible for the weakness of the left side, but no direct correlation was made regarding the lesion of the semilunar lobule and the dysarthria and left-sided numbness. The latter symptomatology probably represented areas of ischemia without evident histologic changes.

Case 5 became confused three days before admission. The confusion gradually subsided until eight days later, when right-sided numbness, disturbance in consciousness, weakness, and nystagmus suddenly appeared. Later, the right leg and arm became paralyzed and a right-sided Babinski sign was elicited. The patient lapsed into a coma on the eighth day and died on the seventeenth day of the final episode. At autopsy, a thrombus was found in the left vertebral artery. An area of encephalomalacia was detected in the posterior portion of the inferior semilunar lobule, affecting the dentate nuclei on the left side also. The cerebellar lesion probably caused the nystagmus. The paralysis and numbness of the right side were not accounted for by the histologic changes but occurred again on the expected side in view of the thrombosis of the left vertebral artery and represent ischemia in that vessel.

Case 6 had a left hemiparesis four years before admission, followed by complete recovery. On the day of admission, the patient suddenly became lethargic, confused, and dysphagic. The left arm and leg became paralyzed, the eyes deviated to the right, and a generalized convulsion ensued. Death occurred on the fifteenth day. In this instance, postmortem examination revealed thrombosis of the right vertebral artery, with encephalomalacia in the right lower pons extending from the midline to a point 3 mm. from the lateral edge and to the restiform body. The pontine lesion caused the weakness of the left side. Occurrence of dysphagia indicated that there was extension of ischemic regions to involve the area of the motor fibers to the tenth nerve.

DISCUSSION

We have collected data within one year on 6 patients with unilateral vertebral artery thrombosis.

Hutchinson and Yates[7] called attention to the likelihood of carotid and/or vertebral insufficiency even though the vessels are not completely occluded and raised the possibility that alteration in the systemic arterial pressure might result in encephalomalacia. We agree with this concept of insufficiency leading to encephalomalacia without actual occlusion of arteries with a thrombus and without the necessary application of a theory of arterial spasm. A reduction in systemic arterial pressure may precipitate the ischemia.

Other papers in the literature[1,5] called attention to vertebral artery occlusion or insufficiency secondary to manipulation of the neck. Tatlow and Bammer[9] found, by angiographic examination in a cadaver, that rotation of the neck may narrow the lumen of the vertebral artery. A similar syndrome associated with thrombosis can occur in patients with no history of nuchal manipulation but who had either diabetes and/or arteriosclerotic hypertensive cardiovascualr disease.

Numerous papers have contributed knowledge regarding disease of the basilar artery.[10–15] In the paper by Millikan and Siekert,[14] the symptoms of basilar artery insufficiency included loss of vision, double vision, ptosis, clouding of consciousness, confusion, unconsciousness, hemiparesis and hemiplegia, dysarthria, dysphagia, sensory disturbance in the face or 1 extremity or half of the body, vertigo, tinnitus, vomiting, unsteadiness, and headache. These authors pointed out that occurrence of the same symptom on opposite sides of the body in definite attacks suggests the diagnosis.

The symptoms and signs previously described as due to basilar artery insufficiency also can be produced by thrombus in a vertebral artery, which may then lead to secondary basilar artery insufficiency. The signs and symptoms in 5 of our patients were primarily unilateral, indicating no significant secondary basilar insufficiency. In case 3, signs were bilateral, suggesting basilar insufficiency secondary to vertebral thrombosis. Since, in the future, management of basilar artery insufficiency may be different from that of thrombosis of a vertebral artery, thrombosis of this type, which may mimic basilar occlusion, must be recognized. Another possibility is that vertebral artery thrombosis may become an indication for therapy with anticoagulant drugs.

This paper is presented to define more clearly the clinical syndrome in occlusion of a single vertebral artery. Therefore, all patients with caroticovertebral insufficiency were omitted. Instead, only patients with actual thrombosis of a single vertebral artery and no significant atheromatous occlusion of other cerebral vessels were selected.

In postmortem interpretation of occlusion of vessels by atheromatous plaques, one of the problems is whether a reasonable judgment can be made as to the antemortem patency of an artery. At autopsy, detection of atheromatous changes that completely or nearly completely occlude a major cerebral vessel in a patient who, in life, had had no cerebral signs or symptoms is not unusual. In defining a syndrome of occlusion of a particular vessel, the presence of thrombosis with evidence of organization appears to be more desirable.

All of the patients presented in this paper had hypertensive cardiovascular disease, diabetes, or both. Associated systemic disease of this type may well be the most common underlying cause in instances of vertebral artery thrombosis.

The vertebral artery generally is considered to supply the pyramidal fibers in the lower pons, the dorsal vagus and glossopharyngeal nuclei, a portion of the hypoglossal nucleus, the nucleus and tractus solitarius, the nucleus and spinal tract of the trigeminal nerve, the ventral and superior dorsal portions of the inferior olive, the dorsal accessory olives, the central tegmental tract, and the lateral portions of the olivocerebellar fibers. In some instances, the inferior cerebellar peduncle, descending root of the vestibular nerve, nucleus ambiguous, spinocerebellar and rubrospinal tracts, and spinothalamic fibers also may be included. When the vertebral arteries fuse at a higher level to form the basilar artery, the nuclei of the sixth and seventh nerves and some of the medial portions of the lower pons also may be supplied by the vertebral arteries.

In the past, a number of syndromes have been ascribed to occlusion of the vertebral arteries. In the syndrome of Avellis, ipsilateral paralysis of the soft palate, pharynx, and larynx and contralateral loss of pain and temperature sensation on the extremities and trunk are observed. In some instances, there is also proprioceptive impairment and diminution in tactile sensation on the contralateral side of the body as well as ipsilateral anesthesia of the pharynx and larynx and loss of taste. Ipsilateral Horner's syndrome and contralateral pyramidal tract signs sometimes occur. Histologic changes involve the spinothalamic tract, the nucleus ambiguous, and, at times, the medial lemniscus and the tractus solitarius. Patients with the syndrome of Cestan-Chenais have paralysis of the soft palate, pharynx, and

larynx and cerebellar asynergy, with Horner's syndrome on the ipsilateral side. Involvement of the corticospinal tract and medial lemniscus produces hemiplegia, loss of proprioception, and, sometimes, diminution in touch sensation on the opposite side of the body. In this case, the lesions are located in the nucleus ambiguous, restiform body, sympathetic fibers, corticospinal tract, and medial lemniscus. The syndrome of Cestan-Chenais differs from Wallenberg's syndrome primarily by the presence of pyramidal signs and medial lemniscus involvement and absence of involvement of pain and temperature sensation. However, variations in these syndromes are frequent, with extension to involvement of the twelfth or eleventh nerve or the spinal tract of the fifth nerve. In Wallenberg's syndrome, the involvement is similar to that of the syndrome of Cestan-Chenais, except that the tenth nerve is not affected. In our patients, the total symptoms and signs commonly incurred in the posterior inferior cerebellar artery occlusion syndrome of Wallenberg did not appear.

In the patients of this study, the thrombus was located above or below the origin of the posterior inferior cerebellar artery, never within the artery.

One would expect that Wallenberg's syndrome would occur when the posterior inferior cerebellar artery is occluded or the thrombus is within the vertebral artery at the origin of the posterior inferior cerebellar artery. When the thrombus is either above or below, blood flow is sufficient so that the syndrome is not complete.

A syndrome of vertebral artery thrombosis is characterized as follows:

- Recurrent central nervous system symptoms, with improvement between episodes, are common. Onset is different from that of posterior inferior cerebellar artery thrombosis but is similar to that of thrombosis of the carotid artery.
- Unilateral weakness occurs, with or without numbness. When symptoms and signs are unilateral, involvement of the vertebral artery alone is likely. When both sides of the body are affected, either basilar artery thrombosis or vertebral artery thrombosis with a secondary basilar artery insufficiency is indicated. Weakness or numbness of 1 side of the body generally precedes a more severe deficiency by only a short time.
- More specific symptoms of the syndrome include vertigo, nausea, vomiting, tinnitus, nystagmus, unilateral deafness, dysphagia, dysarthria, and ataxia. If disturbance of consciousness is rapid, more specific symptoms may not be recognized.

In some of our patients, a direct, point-to-point, clinicopathologic correlation could be made. In other instances, encephalo- or myelomalacia was not found in the areas indicated by the symptoms and signs. Nonetheless, it is in the area of distribution of the vertebral artery on that side and in the same area where the pathologic changes are found when the disease process has progressed to encephalomalacia. We believe that this represents a situation in which ischemia is sufficient to induce clinical signs but in which microscopic changes have not occurred because the ischemia is of short duration or is not severe enough.

In recent years, considerable interest has centered about the subject of thrombosis of carotid arteries. We feel that the possibility of a similar frequency or importance of vertebral artery thrombosis should be entertained. Further, we believe that the syndrome often can be recognized clinically and that the importance of accurate diagnosis of the location of arterial thrombosis will increase as management becomes properly differentiated.

SUMMARY

1] Clinical and pathologic findings in 6 patients with thrombosis of a single vertebral artery are presented. All data were collected within a twelve-month period.

2] Characteristic symptoms and signs that frequently can lead to a clinical diagnosis are described.

3] Vertebral artery thrombosis generally produced unilateral signs, in contrast to the frequent bilateral alternating signs seen in basilar artery thrombosis.

4] Intermittent symptoms were observed in all of the patients described. This is similar to the course of carotid artery thrombosis and differs from the sudden onset usually encountered in posterior inferior cerebellar artery occlusion.

5] In vertebral artery thrombosis and basilar artery insufficiency, symptoms and signs may be identical to those seen in the syndrome of basilar artery thrombosis.

6] All 6 patients had either diabetes or hypertensive cardiovascular disease.

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Karl S. Lashley

If it be permitted one who was not his countryman, and who can boast no more than a friendship with him of some twelve years, I should like to pay my modest tribute to Karl Lashley.

F. M. R. WALSHE

WITH HIS PASSING, there disappears one of the most brilliant exponents of those problems that include psychology and the physiology of the brain. He moved in this difficult territory with an experimental flair, an intellectual poise, and a competence that he shared with few. His contributions to science were of a major order, and lesser men than he have been Nobel Prizemen.

He had the uncommon gift of wearing his learning lightly and of being serious, when occasion demanded, without solemnity. Not less admirable were his intellectual candour and integrity, for he was ready openly to discard earlier views of his own, when his work or that of others seemed to demand this. We may not easily appreciate how unusual is this virtue, for such it is.

It was impossible not to be greatly attracted by these qualities of modesty and integrity. They were as impressive as his contributions to knowledge, which, indeed, they enhanced.

Lashley proclaimed himself a materialist and would have nothing to do with the concept of the soul, which, as he delighted to tell me, the psychologists had long since buried. Yet our debates on this subject were always conducted in a happy vein, and, at our last recent meeting in London, I replied in kind by suggesting that he had got it all wrong, for did not a national anthem positively declare that it was John Brown's body that lay mouldering in the grave, but his soul that went marching along? What loyal American, I asked him, could doubt the oracular quality of this pronouncement?

Seeing him again for the last time, a month ago, after his years of severe illness, it was pleasing to find that although he looked frail, he was as alert, as interested, and as witty as ever, and he seemed to me a mellower and happier man than I had earlier known him. The garment of his "materialism" had worn thin and beneath it I seemed to detect deep human feelings and a high idealism that he would not readily have confessed to, for he hid behind a mask of shyness and of apparent cynicism.

I believe that his philosophy of life had become enriched in the too few years left to him after his illness, years which may well have been amongst his happiest. To Mrs. Lashley, who did so much to brighten the brief Indian summer of his fruitful life, our deep sympathy is offered.

Lashley's high repute in this country was revealed by his election in 1953 to the foreign membership of the Royal Society, but illness had prevented him from coming to London for formal admission.

His brief stay in London in July last made it possible to arrange for his formal admission, and for the signing of his name in the Charter Book, which has been in continuous use since it was opened in 1662 by the signature of the Society's Founder, King Charles the Second.

Lashley knew that in the seventeenth century there had been a Fellow of the name of Clüver. This was found for him, inscribed as "Dethlevu Clüverus," a namesake of his former colleague and his friend, Heinrich Klüver of Chicago.

His pleasure in this private ceremony was manifest, and without reserve, and it was in this happy mood that we took our leave of one another.

Neurology

BOOK REVIEWS

Reticular Formation of the Brain

Edited by Herbert H. Jasper, Lorne D. Proctor, Robert S. Knighton, William C. Noshay, and Russell T. Costello, 766 pp., ill., Little, Brown and Co., Boston, 1958. $16

This symposium, sponsored by the Henry Ford Hospital and held in Detroit, March 14-16, 1957, is a sequel to the symposium on brain mechanisms and consciousness.

Ralph Gerard, who wrote an admirable summary, summed up the function of the reticular formation in one word, *integration*. This is certainly true. Since Magoun and many workers following him have focused their attention on the primacy of the reticular formation, this system now includes the nonspecific nuclei of the thalamus and the related gray matter of the diencephalon, septal region, and amygdala.

The central core of the brain stem plays such a prominent role in behavior that all disciplines dealing with behavior will benefit by the frontal attacks described. The program was divided into neuroanatomy, neurophysiology, and behavioral studies. The papers are well-grouped, and excellent discussions follow main topics. This international symposium brought together the world's pioneers in this field; 36 of whom presented papers.

Anyone who is familiar with the historic development of this subject will agree with George Bishop's analysis of the place of the cortex in a reticular system and heartily endorse his statement when he says, "As I have listened to the papers presented—I have been repeatedly reminded of his (C. Judson Herrick) remarkable analysis of the nervous system of Amblystoma, extended and extrapolated to man – analysis in relation to which current work can only be an elaboration of details."

The pages presented undoubtedly will be the source material for many years to come and serve as a great stimulus to those interested in studying further this almost untouched region of the brain. The question that seems uppermost is how do organisms learn? Material that is learned is retained—but how? And this touches at every point with which neurology deals.

P. G. R.

Comparative Physiology of the Nervous Control of Muscular Contraction

Graham Hoyle. 177 pp., Cambridge University Press, London, 1957. $3

Anatomy of myoneural apparatus is comprehensively described in an extensive comparaitve series beginning with the coelenterates – the first forms in which nervous control of muscle cells appear – through platyhelminthes, nematodes, annelids, molluscs, and other invertebrate phyla.

The author concisely presents the electrical properties of muscle cells in action and at rest, and discusses neuromuscular transmission and end-plate or junction potential. A review follows of neuromuscular phenomena, phylum by phylum, incorporating the present-day concepts of electrical activities – the whole making a masterful chapter on the comparative physiology of the myoneural mechanism. That nine universal principles may be set down as

a basis for the phenomena of neuromuscular transmission in invertebrates and vertebrates is worth special comment. Among the conclusions that can be drawn from this synthesis is the inherent significance of studies on lower animal forms.

In the description of the evolution of the myoneural apparatus, no neat evolutionary story appears, and the author points out that nature has been surprisingly content with its early efforts in myoneural architecture and function. Smooth muscle, striated muscle, and polyneural innervation occur in an amazing range of primitive animal forms.

Because of clarity of style and the extensive, yet judicious, selection of topics, this monograph is both useful and informative. All workers in the fields of comparative neurology and neurophysiology should have it for reference and background data on the neuromuscular mechanism of animal forms beginning with hydra. Obviously, much of the data assembled here can be applied to man. The book is well documented and provided with an index of subject matter and of authors.

A. R. V.

Biology of Neuroglia

Edited by William F. Windle, 340 pp., Charles C Thomas, Springfield, Ill., 1958. $8.50

Observations and opinions on neuroglia are presented by competent investigators.

Structure of neuroglia as seen by the light microscope is discussed by M. E. Scheibel and A. B. Scheibel; electron microscopic study of neuroglia by S. L. Palay; criteria for identification of neuroglia cell types by J. F. Hartman; fibrillar structure of astrocytes by A. Bairati; role of neuroglia cells in myelin formation by B. G. Uzman; perivascular relationship of neuroglia cells by A. Bairati; and fine structure of the neurophil in relation to neuroglia cells by E. W. Dempsey and S. A. Luse.

On the physiology and biochemistry of neuroglia there are discussions of the blood-brain barrier by R. D. Tschirgi; histochemical aspects of neuroglia by C. E. Lumsden; tissue culture studies by C. M. Pomerat; a report on the response of oligodendrocytes to serotonin by M. R. Murray; and histochemical studies of metabolism of neuroglia by C. A. Pope.

In addition to general papers on the direct enumeration of neuroglia cells by J. I. Nurnberger and on the concentration of neuroglia cells by S. R. Korey, there are summarizing presentations on the biology of neuroglia by P. Glees, surveys of the implications of the biology of the neuroglia and microglia cells for clinical neuropathology by R. D. Adams, and on neuroglia cells in relation to neuropathology by A. Wolf. The two latter papers are of particular interest to the clinician.

The experienced reader of symposia who explores the round-table discussions for the occasional sparks that fly from the wheel of free and easy colloquy will be rewarded for his efforts. Checking references is facilitated by a single bibliography for all papers, and the index lists both subject matter and authors.

A. R. V.

Fifty Years of Neurosurgery

Ernest Sachs, 186 pp., Vantage Press, New York City. $3.50

This is the autobiography of one of the pioneer brain surgeons of America told in an informal, homely style. In tracing his career from New York City, where he was born, through college and medical school, to St. Louis, where he practiced surgery of the nervous system for thirty-five years, and finally back to New Haven, where he now resides, Dr. Sachs introduces the reader to many of the great men in education and medicine of the past fifty years. But it is an introduction only, for this book is of Dr. Sachs, his life, his work, his teaching, and his family.

His many friends will find this a delightful story of a rugged pioneer of the midwest. Others may discover interesting anecdotes and tales of the tribulations of the early specialists in neurologic surgery.

For all who wish to read of the struggles and triumphs of the inspired men who founded and developed neurosurgery, this little book is recommended.

A. E. W.

Sequelae of the Arthropod-Borne Encephalitides

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Chairman

PEARCE BAILEY, M.D., and
A. B. BAKER, M.D.
Editors

From the proceedings of a Conference on the Sequelae of the Arthropod-Borne Encephalitides, held at Bethesda, Md., October 16-17, 1957, under the auspices of the National Institute of Neurological Diseases and Blindness

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Editors' Foreword

ONE OF THE MISSIONS of the National Institute of Neurological Diseases and Blindness is to explore and discover methods of prevention of neurologic and sensory disorders. In most instances, the causes of these diseases are unknown, but this is not true for the arthropod-borne encephalitides. Here the viral agents are well known, the vectors are established, and control measures are either available for use or are understood in principle.

It also is well recognized that the sequelae of the acute viral encephalitides contribute to the neurologic disabilities of the people of our nation. A pertinent question raised by Dr. Joseph E. Smadel, chairman of the conference, was, "What proportion of the general group of patients who have had encephalitis suffer from these sequelae?" When more information on this point is available, a better judgment can be made regarding the amount of effort and money that might be spent justifiably in controlling the epidemic encephalitides and their neurologic and psychologic aftermaths.

The purpose of the conference in Bethesda was to provide an up-to-date review of important aspects of the arthropod-borne encephalitides and their sequelae. The conference brought together neurologists, virologists, epidemiologists, and psychologists to assess our present level of knowledge. It was the general concensus that more information was needed on the incidence, severity, and types of residuals that follow these conditions. Means for obtaining such data and new avenues of approach to the problem were discussed.

PEARCE BAILEY, M.D.

A. B. BAKER, M.D.

I. Epidemiology of Arthropod-Borne Encephalitis

Albert B. Sabin

THE ARTHROPOD-BORNE VIRUSES affecting the central nervous system can be divided into 2 groups: the tick-borne and the mosquito-borne. Of the former, the most important virus is that associated with Russian spring-summer encephalitis and other syndromes which, from available current knowledge, are present throughout the Eurasian area of the world. At first, it was thought that this infection was limited chiefly to the Far East and Siberia. Newer information shows that this is not true. Diseases caused by this virus or group of viruses have been identified in many areas of the U.S.S.R., as far west as Leningrad, as well as in Sweden and Central Europe. Because of its very wide distribution in Central European countries, the disease has also been called Central European encephalitis. A few human cases caused by the related louping-ill virus of sheep have been reported in the British Isles.

The vector believed to transmit this group of viruses varies in different parts of the Eurasian continent. In the Far East, the vector is said to be the tick *Ixodes persulcatus*, which is found in a large area of the Far East and in the Siberian forests. Its habitat extends into the European part of the Soviet Union and Central Europe, where it is gradually replaced by another tick called *Ixodes ricinus*.

The tick transmitting Russian spring-summer encephalitis has a tendency to bite people around the neck and shoulder girdle. It is, perhaps, for this reason that one of the striking clinical manifestations of this disease is paralysis of the neck and shoulder muscles. In the Far East, human infections begin in late April or May and usually terminate around June. The season for *Ixodes ricinus* is longer and may extend to October.

Apparently, the ticks themselves can be the ultimate reservoir of the virus. According to Russian studies, the virus is transmitted through the eggs from one generation to the other. As long as the tick survives, the virus also survives. These ticks tend to live on woodland animals and birds.

Another cycle has been described in Europe in which ticks are not involved. According to the Russian work, the ticks may bite goats which become infected and excrete the virus in their milk. Individuals who drink unpasteurized milk from these goats then may develop the disease.*

The second of the tick-borne virus infections is Colorado tick fever. Involvement of the nervous system by this virus has been reported recently by Dr. Eklund. According to his work, this virus has been found in 10 states in the United States and has produced clinical encephalitis which, in certain cases, has been fatal. The tick carrying this virus is *Dermacentor andersoni*. To date, no evidence of transovarian transmission of this virus has been found.

The second group of arthropod-borne infections of the nervous system are those caused by mosquito-borne viruses. These may be divided into groups A and B. This classification is based upon certain antigenic relationships demonstrable by the hemagglutination test.

Group A contains the Western, Eastern, and Venezuelan equine encephalitis viruses. These are, apparently, all Western Hemisphere viruses.

The important natural vector for the Western equine encephalitis virus is the mosquito, *Culex tarsalis*. Birds are the preferred hosts, although the mosquitoes may bite horses or larger animals when the number of birds is inadequate. The significance of this fact is that, in order for this infection to spill over into man, the population of *Culex tarsalis* must be tremendous, and the infection rate in these mosquitoes must be very high.

*Recent studies by van Tongeren of Holland have raised doubts about the role of ticks as vectors of Central European encephalitis. Further studies are needed to elucidate this question.

Although human infection with Western equine encephalitis virus appears to have certain geographic limitations within the United States, it has been observed that birds and mosquitoes in the East have been infected even though no human cases have been recorded, thus far, in these areas.

The important natural vector for the Eastern equine virus apparently is the mosquito, *Culisetta melanura*. This mosquito also bites birds predominantly, then horses, and, rarely man. Once infection with this virus is introduced among pheasants, it may pass from bird to bird without mosquitoes. There is a question as to whether this is transmission by direct contact or whether some other intermediate host perpetuates the virus within and among these birds.

The vector for Venezuelan equine encephalitis virus is the mosquito, *Mansonia titillans*. As regards recognized disease, the infection of horses is by far the most important. Infection of man is probably, as a rule, apparent rather than inapparent and in most instances characterized only by a febrile systemic illness. Only a few cases of encephalitis have been recorded in human beings thus far, and these were fatal.

Group B mosquito-borne viruses may be divided into those found in the Western Hemisphere and those found in the Far East. The chief encephalitis virus of the Western Hemisphere is the St. Louis virus, which has different mosquito vectors in different parts of the United States. In the Western United States, the important natural vector is *Culex tarsalis*, while in the Middle West and the Ohio valley it is *Culex pipiens*. Birds and domestic animals again attract the largest number of these mosquitoes. Tremendous populations of mosquitoes are necessary before human infections appear.

Group B mosquito-borne encephalitis viruses of the Far East are chiefly Japanese B encephalitis and, less commonly, Murray Valley and West Nile viruses. The mosquito of importance in the transmission of Japanese B encephalitis is *Culex tritaeniorhynchus*. This mosquito has a very limited season, and does not appear in great numbers until flooding of the rice paddies permits breeding on a large scale. Since the paddies are not flooded until June, the population of this mosquito does not build up until July and then its life span is very short.

This mosquito, again, predominantly bites birds and larger animals, although the exact role of birds in transmission is unknown. For example, in Okinawa in 1945, two-thirds of a force of 250,000 American troops occupied the southern end of the island and one-third lived in close association with the native population and their domestic animals, almost all of whom had been moved to the northern part of the Island. All proved cases of Japanese B encephalitis occurred among the 70,000 men who were stationed in the north and none was found among those stationed in the south. If birds played a role in the transmission of this disease, infections should have occurred in both the south and the north. However, mosquito control may have been easier in the plains of the south than in the mountains of the north.

One of the chief questions regarding mosquito-borne virus infections of the nervous system is how the viruses survive during the winter and where the first mosquito emerging during the summer obtains its viral infection. No transovarian passage of the virus from one generation of mosquitoes to the next has been demonstrated, and mosquitoes that obtain a blood meal before hibernating do not survive. Possible explanations include:

1] That the virus persists in birds during the winter and becomes available to mosquitoes again during the proper period of the year.

2] That migratory birds carry the virus from tropical and subtropical regions to the temperate zone.

3] That mites may serve as hosts for wintering of the virus. Mites may potentially transmit viruses through their eggs from one generation to the next. Mites feeding on a virus suspension or a chick that has virus in its blood may take up some of the virus, but evidence that it can transmit the virus to birds is not conclusive.

Another interesting fact about the arthropod-borne encephalitides in man is that while infection can be extremely widespread, only a few individuals show clinical evidence of disease. This was shown most strikingly by a study in China where more than 80% of young

adults in one area had neutralizing antibodies for Japanese B encephalitis but very few cases had been reported or recognized.

Once an individual has become infected, a number of factors may determine the occurrence of encephalitis: [1] genetic factors in the host that influence the level of virus multiplication; [2] the strain of virus that infects man, since it has been reported that some strains have a greater capacity for producing viremia and clinical manifestations in peripherally inoculated older mice than others; and, finally [3] the presence of an associated parasitic infestation or other involvement of the nervous system that may make the nervous system more susceptible to viral invasion.

II. Western Equine Encephalitis

Clinical Features: **A. B. Baker**

THIS DISEASE affects individuals in all age groups and has been reported in both children and infants. The incubation period has not been definitely established but appears to be around two weeks.

The onset is usually sudden, but not explosive, with generalized malaise and mild headache, followed occasionally by some nausea and vomiting. The temperature becomes moderately elevated, and chills may occur. After a few days, the headache increases in intensity often becoming constant and generalized, with extension to the occipital region or down the back of the neck. Restlessness develops within a few days and is often associated with lassitude and drowsiness.

In children, the entire encephalitic picture may be ushered in by a seizure associated with drowsiness or extreme vertigo. Drowsiness may progress to a fairly severe lethargy; however, the patient usually responds to sufficiently intense stimuli. In some instances, photophobia and vertigo may become a prominent part of the syndrome.

The intensity of these general manifestations varies from patient to patient. Headache is one of the most common symptoms and is present in all cases. Typically, the fever is constantly low grade, often being highest during the first week of the illness but rarely rising above 103° F. Mental symptoms are very common and among the most frequent manifestations. In adults, lassitude, apathy, drowsiness, and finally complete or partial unresponsiveness may occur. In children, a period of irritability and restlessness frequently appears after days of drowsiness or, in some cases, even coma.

Ordinarily, the symptoms persist about ten days and then gradually subside. In more severe cases, the temperature rises to 105 to 106° F., the headaches grow intense, and the sensorium becomes cloudy with disorientation in all fields. This lethargy commonly passes into stupor alternating with extreme restlessness. In fatal cases, the course is usually rapid, death often occurring four to seven days after onset.

Physical findings vary in nature and degree, depending upon the part of the nervous system that is involved. The only constant finding is a mild stiffness of the neck associated with a positive Kernig's sign. Pathologic reflexes are encountered and often fluctuate from day to day or even from hour to hour. Severe generalized muscular weakness may be present and often persists long after all other disturbances have subsided. Hyporeflexia has often been noted. In children, muscular rigidity, involuntary movements, and mild transient muscle weakness or paralysis are common. The cerebrospinal fluid is usually normal, except for a mild increase in cells to as high as 200. Monocytes usually predominate. The spinal fluid protein is normal but may be slightly increased.

In many cases of Western equine encephalitis, clinical manifestations of nervous system involvement are so mild that they are often overlooked. Neurologic manifestations are frequently entirely absent and, at best, manifested only by mild headache, slightly elevated temperature, and occasionally a questionable cervical rigidity. Spinal puncture reveals the

nature of the encephalitic process. In most cases, respiratory or gastrointestinal manifestations predominate. These patients may have sore throat, grippy aches and pains, or vomiting, diarrhea, abdominal distention, and abdominal discomfort.

Pathology: **Webb Haymaker**

Outstanding pathologically are the many foci of rarefaction necrosis, numerous in the striatum and fewer in the globus pallidus, cerebral cortex, thalamus, and pontile tegmentum, in that order of decreasing frequency. Less severe focal lesions, characterized by loosening of tissue, are sometimes related to vessels, sometimes not. Vessels within foci seem unaffected.

Many foci of tissue rarefaction are free from reactive cells, while others contain scattered pleomorphic reactive cells, including macrophages. A fair number of these foci contain neutrophilic leukocytes, occasionally in so high a proportion that the foci can be referred to as "abscesses." Moreover, there are neutrophils, perivascularly and in the surrounding tissue, representing a rather low-grade focal acute cerebritis. Glial or gliomesenchymal neuronophagic nodules are, in general, sparse. The white matter is spared except in cases of long duration (nineteen days), in which patchy astrocytosis occurs, undoubtedly as a result of edema.

Perivascular collections of lymphocytes and ameboid cells also are noted, with lymphocytes predominating around large veins and ameboid cells around smaller vessels. Perivascular tissue breakdown may also occur, and proliferated oligodendroglia and microglia and invasive mesenchymal cells accumulate within such foci. Perivascular collections of reactive cells, as well as breakdown of perivascular nervous tissue of varying degree, are found in the striatum, pallidum, thalamus, substantia nigra, mesencephalic tegmentum, medulla oblongata, and here and there in the cerebral cortex. The inferior olivary nucleus contains scattered gliomesenchymal nodules.

Occasional cases of chronic Western equine encephalitis have been characterized by severe cystic transformation as well as by rather pronounced thickening of the walls of scattered small vessels in the basal ganglia, cerebral white matter, and cerebral cortex. The "cysts" might have resulted from continued enlargement of foci of rarefaction necrosis or from oligemia secondary to thickening of vascular walls, but since cystic transformation of this kind is unprecedented in the viral encephalitides, it seems more logical to assume that it represents a coincidental complicating morbid condition.

Clinical Sequelae: **Knox H. Finley**

The incidence and severity of sequelae of Western equine and St. Louis encephalitis have been found to be related to age.* Sequelae among very young infants are frequent and severe, but incidence and severity decrease rapidly after the age of 1 year. All infants under 1 year of age with encephalitis in Finley's group had the Western equine type. St. Louis encephalitis is practically never seen in this age group.

Sequelae in infants consist of motor impairment (pyramidal, extrapyramidal, and cerebellar), behavior retardation, and convulsions. In children with severe damage, all three types of sequelae occur. In children with less severe damage, one type may appear without the others.

The younger the patient at the time of the acute illness, the more frequent and severe the sequelae. In 18 of Finley's patients, who were less than 1 month of age at the onset of the illness, 10, or 56%, had residuals; in all, the residuals were severe. Of 49 infants who were 1 to 2 months old at onset, 20, or 41%. had residuals, but these were severe in only 8. Only 22% of infants (4 of 18) between 2 to 3 months of age had residuals; in half, the residuals were severe. With each succeeding month of age past 3 months, patients had sequelae with less frequency and of decreasing severity. Of 24 children between the ages of 1 and 2 years, none developed either motor or behavior problems and only 6 had convulsions.

Occasionally, older children showed sequelae — sometimes severe in nature. The most

*According to Finley and associates in a four-year study of 634 persons in California

common was a mild paresis of one or more extremities.

For some time after the acute illness, adult patients complained of such subjective complaints as nervousness, irritability, easy fatigability, headache, and tremulousness; however, these symptoms usually disappeared without residuals after a few months to two years.

Some evidence shows that sequelae are less frequent and less severe after St. Louis encephalitis than after Western equine encephalitis. This is a somewhat weighted finding because all infant patients had Western equine infections; however, even in older children and adults there seem to be slightly more sequelae after Western equine than after St. Louis encephalitis.

Of especial interest have been the findings with regard to recurrence of convulsions after the acute illness. Convulsions are very common during the acute stage in infants, occurring in almost 100% of babies less than 1 month of age and in approximately 90% of those under 1 year old. Convulsions recur in approximately one-third of patients less than 1 year of age at onset. On the other hand, convulsions have not occurred after acute illness in any patients free of convulsions during the illness, regardless of the age at onset.

***Pathologic Sequelae:* A. B. Baker**

Baker and his group have described 3 cases of chronic Western equine encephalitis that came to autopsy. One, a child who recovered from the acute illness, showed a progressive downhill course over a period of three years and died. The virus was isolated during the acute stage of the disease. The other two cases were adults in whom serologic tests indicated Western equine encephalitis. The findings in all cases were similar.

Many of the small vessels showed endothelial proliferation with almost complete occlusion of the lumen. The smaller vessels were also often occluded by deposition of calcium within the vessel wall and lumen. Larger vessels showed complete thrombotic occlusion by inflammatory elements, suggesting that a definite vasculitis produces the vascular changes and occlusion.

Tissue changes were consistent with vascular alterations. Scattered throughout were small areas of focal necrosis that often contained phagocytic elements. In scattered areas, large cavities replaced extensive areas of brain tissue. Some cavities actually replaced portions of an entire cerebral hemisphere. As a result, rather severe clinical residuals can be expected after some cases of Western equine disease.

III. Eastern Equine Encephalitis

***Clinical Features:* Roy F. Feemster**

EASTERN EQUINE ENCEPHALITIS predominates in the young age group, about two-thirds of the patients being under the age of 2 years. Clinically, the disease is fulminating. The onset is very abrupt, with extremely high fever, lethargy, vomiting, and convulsions. The patient is gravely ill within one to two days.

The most common symptom is stupor or coma, often associated with or followed by convulsions that become severe and generalized. Particularly in young individuals, convulsions may be the presenting symptom. In addition, the patient may have a stiff neck, generalized rigidity, twitching, and irritability. The temperature is usually high, ranging between 102 and 104° F. The pressure of the cerebral spinal fluid is often increased, and pleocytosis often exceeds 100 cells per cubic millimeter.

The mortality rate in patients over 10 years of age is 75%, under 10 approximately 68%. Surviving patients under 10 years of age often have strikingly severe neurologic residuals, such as mental retardation, hemiparesis, aphasia, and emotional instability.

***Pathology:* Webb Haymaker**

An outstanding feature is the predominance of neutrophilic leukocytes in the infiltrates. Focal or diffuse accumulations of neutrophils and activated histiocytes are prominent in the

leptomeninges. The cerebral cortex, particularly that of the frontal and occipital lobes and the hippocampus, is profoundly affected.

Foci of tissue damage are often found in the form of rarefaction necrosis and are permeated not only by neutrophilic leukocytes but also by pleomorphic ameboid cells. Neuronolysis, usually with neutrophilic leukocytes nearby, is very common in fulminant cases.

Large perivascular collections of neutrophils and ameboid cells (mostly activated histiocytes) are frequently detected in the white matter in regions of cortical involvement. Other sites of predilection are the thalamus, putamen, substantia nigra, and pars basilaris pontis. The medulla oblongata and spinal cord are only slightly affected, and the cerebellum apparently is spared except for occasional "shrubs" emanating from the Purkinje cell layer.

In a case of twenty-three days' duration, the neutrophilic leukocytes had disappeared and the affected regions of the cerebral cortex were reduced to a mass of reactive mononuclear cells. In some regions, almost the entire width of the cortex was thus affected. Large perivascular cuffs of lymphocytes and ameboid cells were widespread but seen most frequently in the cerebral cortex. Changes of the same kind were found in the thalamus but were most striking in the substantia nigra, which was almost completely destroyed.

Sequelae: Roy F. Feemster

In a disease with such a fulminating course as Eastern equine encephalitis, severe sequelae would be expected in patients who survive.

Of a total of 50 patients studied, 16 survived the acute illness. Of these, 8 were under 5 years of age; 6 had very severe sequelae. Only 1 of the survivors in this age group appeared to have recovered. In surviving patients between the ages of 5 and 9 years, sequelae were much less severe. Of 4 patients over the age of 40 years who survived, only 1 manifested mild sequelae.

It would appear that patients under 10 years of age have a better chance of surviving the acute illness but a greater chance of developing severe disabling residuals. The latter consist of mental retardation, strabismus, convulsions, lack of emotional control, hemiplegia, impaired vision, partial deafness, and speech disorders.

IV. St. Louis Encephalitis

Clinical Features: G. O. Broun

St. Louis encephalitis is usually of sudden onset. It is characterized by a rapid rise in temperature to 102 to 106° F., with some signs of meningeal irritation and frequently nausea and vomiting. While the temperature curve is irregular, fever usually is highest within the first three to five days after onset. The temperature then falls rather quickly, reaching normal in about one week.

Shortly after the illness begins, symptoms such as drowsiness, stupor, mental confusion, and delirium are noted. Evidence of cranial nerve involvement is relatively rare. Diplopia occurs in less than 10% of cases and usually is transitory. Some muscular rigidity occurs often, and muscle tremors are fairly common. Abdominal, cremasteric, and deep tendon reflexes many times are unequal and occasionally suppressed. Pathologic toe signs are noted in almost all patients but vary in location and type even within brief periods of time.

The peripheral blood shows few pathologic alterations other than occasional moderate polymorphonuclear leukocytosis. Urinalysis is essentially normal, with the exception of a few instances of slight albuminuria and, still more rarely, the presence of leukocytes, erythrocytes, and casts. Elevation of the blood nonprotein nitrogen is noted chiefly in cases with dehydration. Slightly elevated blood sugar levels sometimes are noted, but glycosuria, except in known diabetics, is very rare.

The cell count of the spinal fluid is almost always elevated during the febrile period. The

elevation is moderate, being between 7 and 250 cells in over 90% of cases, with higher counts in only about 6%. Rarely is the count above 1,000 cells. Lymphocytes predominate in practically all instances. The spinal fluid is generally clear, but rarely slightly turbid or bloody, often with some increase in pressure. The protein of this fluid in many cases is slightly increased. Sugar content usually is normal or occasionally slightly elevated.

No particular tendency to false-positive Wassermann or Kahn tests is noted in either spinal fluid or blood. The colloidal gold test quite constantly shows moderate change, with a tabetic type of curve in most instances. This change persists for some time into convalescence.

The morbidity and mortality rate of St. Louis encephalitis increase steadily with age, constituting a unique and puzzling feature of this disease. The mortality is quite low in patients under 40 years of age. The mortality is markedly increased in persons with arteriosclerosis and hypertensive vascular disease. In hypertensive patients between 38 and 58 years of age, the mortality is more than 9 times that of normotensive persons and in individuals between 59 and 84 years, it is more than twice as great. Further study is needed regarding [1] whether vascular lesions facilitate localization of the virus in the central nervous system and [2] whether the perivascular infiltrations in the brain that are characteristic of the pathology of the disease exacerbate preexisting vascular damage.

Pathology: Webb Haymaker

The lesions of St. Louis encephalitis predominate in the thalamus and substantia nigra. The cerebral cortex is slightly to moderately affected, as are the molecular and Purkinje-cell layers and dentate nucleus of the cerebellum. Structures less frequently and less severely involved are the hypothalamus, tegmentum, pars basilaris pontis, reticular formation, and inferior olivary nucleus. In most cases, the anterior horns of the spinal cord are moderately affected, with the lesions mainly perivascular in distribution. There is usually little neuronophagia. In fulminant cases of approximately twenty-four hours' duration, numerous nerve cells are selectively necrotic, but the necrosis induces little reactive cellular response.

The basic lesion appears to be perivascular. There is a loosening of tissue but seldom any rarefaction necrosis. Macrophages displaying karyorrhexis are frequent in the loosened tissue. The relative intensity of the pathologic lesions in different regions of the central nervous system – in decreasing order of severity – are midbrain, thalamus, striatum, rolandic cortex, pons, medulla oblongata, cerebellum, frontal cortex, and temporal cortex. Only occasionally has the cerebral white matter been found to be significantly affected.

Sequelae: J. Earl Smith

Bredeck and associates made 3 follow-up studies of patients who had encephalitis during the St. Louis epidemic in 1933. The first study started early in December 1933 and was completed on March 1, 1934. This study was based on a questionnaire sent to 874 survivors; 375 reports were received. This was considered unsatisfactory because some of the reports were not clear as to whether the symptoms of the patients were really aftereffects of the encephalitis or whether they had been present in the same degree before the illness. In some instances, it was evident that symptoms during the acute stage of the disease were included.

The second study – again by questionaire only – was carried on during the fall of 1934 and the spring of 1935. The number of patients reporting a specific symptom are listed in Table 1 according to the number of times the symptom was recorded on the questionnaire. Obviously the numbers in themselves do not reflect the seriousness and long-term effects of a recorded symptom.

After an analysis of the second follow-up had been completed, it became obvious to the committee that a third follow-up study would be necessary, primarily for the purpose of making a reexamination at some future date (1936) of patients who presented not only residual symptoms but also organic defects. There were 31 such patients.

The health commissioner, at that time, the late Dr. Joseph F. Bredeck, appointed for this purpose a special medical team consisting of

an internist, a pediatrician, a neurologist, and the assistant health commissioner (also an internist). Of the 31 patients, 18 showed evidence of definite organic defects, as shown in Table 2.

This examining team made this rather significant statement: "The most important disturbance of the motor nervous mechanism noted was difficulty in walking."

Outstanding general symptoms are listed in Table 3. Here, again, one would be more concerned with the serious nature of specific symptoms. The special examining team, in commenting on subjective nervous complaints in general, pointed out that such conditions as nervous excitability, irritability, loss of memory, and drowsiness were the most important, percentagewise. They further stated that: "Some of these complaints were present prior to the attack of encephalitis. Subjective nervous complaints, nevertheless, would appear to be by far the most common residuals of the St. Louis type of encephalitis. They are of sufficient severity to cause complete or serious incapacity in but few instances." The "few instances" are hardly a conclusion because they are based on too few cases and altogether too few studies of the total problem.

The St. Louis area, that is St. Louis City plus St. Louis County, experienced another sizable outbreak of encephalitis in the late summer and early fall of 1937. Totals of 338 resident cases and 89 deaths were reported to the St. Louis Health Division. This compared with totals of 577 resident cases and 130 resident deaths reported during the 1933 outbreak. The reported city cases in 1937 represent approximately a 60% relationship to the 1933 city incidence.

It is rather ironical that, while the 1933 outbreak attracted world-wide attention and an unusual concentration of workers from many specialized fields in this country, in 1937 practically no one (exclusive of some St. Louis workers) came to see the show. This, in spite of the fact that no published reports on the role played by certain species of mosquitoes in the transmission of the disease to human beings had as yet been shown. These published reports began about 1938, as intelligent deductions were followed by a flood of definitive reports.

TABLE 1

ANALYSIS OF THE MOST SIGNIFICANT RESIDUAL SYMPTOMS NOTED IN FOLLOW-UP OF 331 PATIENTS 12 TO 18 MONTHS AFTER INFECTION

Number of cases	*Symptoms noted in follow-up*
164	Nervousness
135	Headache
124	Easy fatigability
99	Excitability
96	Weakness
91	Forgetfulness
88	Dizziness
85	Irritability
78	General pain
71	Drowsiness
70	Difficulty in walking
70	Feeling of depression
65	Sleeplessness
59	Inability to concentrate
49	Difficulty in hearing
47	Double vision
32	Muscular tremors
16	Disturbance in speech
16	Difficulty in smelling
14	Difference in taste of food

TABLE 2

NATURE OF ORGANIC DEFECTS FOUND IN 18 PATIENTS THREE YEARS AFTER INFECTION

Number	*Organic defects*
6	Defect in speech
6	Difficulty in walking
6	Disturbances in vision
3	Positive Romberg sign
2	Deafness
1	Positive Oppenheim and Babinski signs
1	Change in acuity of smell
1	Lateral nystagmus
1	Paralysis of both lower extremities
1	Partial paralysis of upper extremities
1	Right hemiplegia
1	Epileptiform convulsions

TABLE 3

OUTSTANDING GENERAL SYMPTOMS IN 18 PATIENTS WITH ORGANIC DEFECTS

Impaired memory	Dizziness
Nervousness	Inability to walk firmly
Irritability	Inability to work
Weakness	Sleeplessness

TABLE 4

PHYSICAL FINDINGS IN 52 PATIENTS WITH EPIDEMIC ENCEPHALITIS

Physical findings	*Per cent of positive cases*	
Muscle weakness or paralysis	A	20
	B	10
	C	20
Muscle tremors	A	50
	B	48
	C	40
Muscle spasticity	A	27
	B	11
	C	5
Kernig	A	8
	B	3
	C	0
Ankle clonus	A	0
	B	0
	C	5
Nystagmus	A	10
	B	10
	C	5
Romberg	A	0
	B	15
	C	10
Superficial reflexes, hyperactive	A	0
	B	0
	C	10
Superficial reflexes, unequal	A	15
	B	10
	C	10
Superficial reflexes, decreased or absent	A	40
	B	27
	C	20
Babinski	A	55
	B	15
	C	5
Oppenheim	A	50
	B	18
	C	2
Gordon	A	45
	B	14
	C	2
Chaddock	A	18
	B	2
	C	0
Decreased vibratory sense	A	Uncertain
	B	15
	C	17
Tendon reflexes, hyperactive	A	18
	B	15
	C	27
Tendon reflexes, unequal	A	29
	B	39
	C	25
Tendon reflexes, decreased or absent	A	25
	B	10
	C	7

TABLE 5

GENERAL NEUROLOGIC MANIFESTATIONS IN 52 PATIENTS WITH EPIDEMIC ENCEPHALITIS

Symptoms or physical findings	*Per cent of positive cases*	
Drowsiness	A	47
	B	9
	C	30
Stupor	A	15
	B	0
	C	3
Irritability	A	16
	B	40
	C	49
Excitability	A	0
	B	0
	C	15
Mental confusion	A	14
	B	0
	C	5
Irrationality	A	25
	B	4
	C	5
Delirium	A	15
	B	0
	C	0
Mania	A	5
	B	0
	C	0
Memory defect	A	20
	B	30
	C	60
Dizziness	A	20
	B	38
	C	40
Nervousness	A	Uncertain
	B	25
	C	43
Feeling of depression	A	0
	B	0
	C	15
Restlessness	A	0
	B	5
	C	15
Difficulty in walking	A	Uncertain
	B	10
	C	15

A = During acute illness B = Four months later
C = One year later

Tables 4, 5, and 6 were made available through the courtesy of Dr. G. O. Broun, Professor of Internal Medicine, St. Louis University School of Medicine. The data pertain to his one year observation of patients with St. Louis type encephalitis during the 1937 outbreak.

TABLE 6

GRANIAL NERVE INVOLVEMENT IN 52 PATIENTS WITH EPIDEMIC ENCEPHALITIS

Symptoms or physical findings	*Per cent of positive cases*	*Symptoms or physical findings*	*Per cent of positive cases*
Double vision	A 6 B 6 C 5	Facial weakness	A 3 B 13 C 18
Gross visual changes	A Uncertain B 45 C 32	Disturbance in taste	A 0 B 15 C 3
Photophobia	A 3 B 9 C 0	Appetite affected	A 0 B 5 C 4
Unequal pupils	A 10 B 10 C 10	Speech disturbance	A 8 B 13 C 6
Ear symptoms	A 10 B 25 C 32	Difficulty in writing	A Uncertain B 20 C 0
Disturbance in smell	A 0 B 0 C 0	Tongue tremor	A 65 B 25 C 30

A = During acute illness B = Four months later C = One year later

V. Japanese Encephalitis

***Clinical Features:* O. M. Weaver**

THIS DISEASE is characterized by an abrupt onset and a very stormy course with cerebral and meningeal manifestations and transient ocular phenomena. Prodromal symptoms are uncommon but consist of headache, malaise, anorexia, and vomiting, suddenly becoming markedly exaggerated after a few days.

The temperature rises acutely to alarming heights and is one of the characteristic features. With the elevation of temperature, the headaches become worse and mental symptoms appear in the form of confusion, disorientation, severe delirium with hyperkinetic phenomenon, or somnolence and coma. Often, coma progresses to stupor and alternates with delirium.

Generalized and focal motor weakness is a constant feature. Muscle fatigue and weakness, unaccompanied by muscle atrophy or flaccidity, reach a peak at about the first week of illness and generally confine the patient to bed for a period of seventeen days. Localized weakness of the musculature occurs in about one-third of cases, involving primarily the upper muscles. Sensory disturbances may be noted but are generally mild and consist of hypesthesia and paresthesias of a segmental distribution. Nystagmus, diplopia, and blurring of vision are not frequent but may occur. Occasionally the patient develops a definite facial paralysis which, on recovery, may be followed by chronic twitching of the facial musculature. Frequently, during the acute illness, a peculiar conjunctival discharge develops which, on study, is found to be of fatty material.

In fatal cases, the patient passes rapidly into coma, with death generally occurring after seven to ten days. In nonfatal cases, the fever is not as high and the mental and meningeal disturbances are usually less severe. The temperature begins to fall after a week and there is a gradual recovery in a two- to three-week period. Cerebral spinal fluid is clear but with moderate pleocytosis up to 250 cells, sometimes higher. In the early part of the disease, there may be a predominance of polymorphonuclears and later mononuclears. In most cases, a high pleocytosis in fluid is present before the fifth day of the illness.

***Pathology:* Webb Haymaker**

Japanese encephalitis is almost always characterized by intense neuronophagia. Myriad gliomesenchymal nodules, mostly neuronophagic, are found in the cerebral cortex and the molecular and Purkinje cell layers of the cerebellum. In some structures, chiefly the thalamus and substantia nigra, foci of tissue breakdown are found, with accumulation of reactive ameboid cells. Other parts of the central nervous system affected are the anterior perforated substance, tegmentum and reticular formation of the brain stem, pars basilaris pontis, inferior olivary nucleus, and, in less measure, the hypothalamus, striatum, and pallidum. Multiple foci of rarefaction necrosis are common, mainly in the striatum and cerebral cortex. In the brain stem and gray matter of the spinal cord, as well as in the structure mentioned, lymphocytes and ameboid cells accumulate perivascularly, with ameboid cells frequently invading adjacent damaged nervous tissue.

When the course continues as long as three months, the most conspicuous change is usually in the thalamus. Small and large areas of devastated tissue are partly replaced by macrophages and surrounded by a wall of glia. In areas of predilection, focal gliosis is noted with little inflammatory cell reaction. The cerebral cortex shows a varying number of foci, deficient in nerve cells, which contain rod cells and enlarged astrocytic nuclei. Calcified vessel walls associated with damaged nervous tissue have been noted in the cerebral cortex, globus pallidus, thalamus, red nucleus, and substantia nigra.

***Sequelae:* O. M. Weaver, S. Pieper, and R. Kurland**

The residuals of Japanese encephalitis consist primarily of intellectual impairment, confusion, loss of moral values, severe emotional instability, and memory loss. Weaver and associates studied 65 proved cases for the appearance of these residuals. At the end of ten weeks, 12 had important sequelae. By the end of five months, 8 of these had recovered. Thus, only 4, or 6.15%, showed sufficient residuals to warrant separation from service.

Psychological studies were done on a series of 108 cases. Such studies indicated definite organic residuals in 10, or 9.3%. In 5, or 4.7%, the organic mental residuals were sufficient to warrant separation from the service. Neurotic symptoms, consisting of tenseness, hyperhidrosis, insomnia, restlessness, and frequent battle dreams, were manifest at the time of the examination in 15 or 13.9%.* Only 9 patients of this entire group were unable to return to duty within a year after the onset of illness, and, in 4, reasons other than residuals of encephalitis were implicated.

Edgren and Hammon and associates observed 27 hospitalized patients with Japanese encephalitis in Guam. Almost ten years later these patients were reevaluated by Pieper and Kurland. Only 1 was over 20 years of age; 11 were less than 5 years of age; 6 were 5 to 9 years of age; and 9 were 10 to 19 years of age. Of the patients, 15 had Japanese B encephalitis and 12 were considered as having Japanese B encephalitis in conjunction with a recent mumps infection. No difference in the frequency of sequelae in the two groups was noted, nor was there appreciable difference in sequelae between the two sexes.

Of the 27 patients with Japanese B encephalitis, death occurred in 2, or 7.4%; both were children under 5 years of age. Of the remaining 25 patients, follow-up examinations were completed on 23; the other 2 are believed to be free of significant sequelae on the basis of reports from their parents. Of the 25, 15 suffered no sequelae of the encephalitis. However, 2 of the 15 may have been injured or predisposed to further brain injury, but circumstances hindered evaluation of the degree of brain injury possibly resulting from the encephalitis. (One of the 2 was a mentally retarded deaf mute with bilateral extensor plantar responses who was said to be no worse after the encephalitis; the other had apparently recovered from encephalitis but had a head injury in 1953 followed by grand mal seizures and moderate mental deterioration).

In the remaining 10 patients, 8 (32% of the total) had neurologic or intellectual defects and 2 (8%) had psychiatric complaints. In 1 patient brain stem and cerebellar dysfunction were evident. Convulsive seizures, left hemi-

*These neurotic or anxiety symptoms can be considered largely the result of combat in which these soldiers were engaged at the time of onset of their illness.

paresis, and cortical sensory impairment occurred in 1 patient, as demonstrated by moderate astereognosis, poor 2-point discrimination, and weakness, spasticity, and slight atrophy of the left upper extremity. Examinations were negative in 2 patients, except for bilateral extensor plantar responses; 1 was somewhat subnormal on mental testing and had bilateral extensor plantar responses.

Mental retardation was found in 3 patients; 1 was severely retarded and had moderate spasticity of all limbs and strabismus due to right lateral rectus muscle weakness; another patient was moderately retarded and responded poorly to traced figure and 2-point discrimination tests; the third had poor memory, recall, general information, and ability to calculate.

Symptoms suggestive of psychologic dysfunction were noted in 2 patients who have been included as having "sequelae"; 1 stuttered and was enuretic, whether related to the encephalitis or not is uncertain; 1 other patient had complaints more suggestive of organic damage with occasional blackout spells and repetitive auditory and visual hallucinations, the latter predominantly in the left peripheral field.

The reported frequency and severity of sequelae of acute infectious encephalitis depend upon numerous variables, including the type and virulence of the organism, the availability and utilization of medical care by the affected population, and the adequacy of later examinations. The high fatality rate (33% or higher) and the low sequelaes rates (3 to 14%) reported from Japanese sources contrast with those in this study – 7.4% fatality rate and at least 32% sequelae rate. Among native and U.S. military personnel observed in the Far East after World War II, the case fatality was reported at about 10% and the clinical disability about 20% six months after the onset of the acute episode.

VI. Colorado Tick Fever

Carl Eklund

COLORADO TICK FEVER, a virus disease spread by the Rocky Mountain wood tick, *Dermacentor andersoni*, in the mountainous areas of the West, generally has been regarded as a benign, dengue-like disease. However, the virus of Colorado tick fever now has been isolated from patients affected with mild and severe central nervous system symptoms.

Clinical features. The severe form of the illness is characterized by the acute onset of a very high fever, intense frontal headache, stiff neck, and a rash. The rash usually is maculopapular and appears on the body, extremities, and face, sparing the palms and soles. Rarely, the rash may become purpuric and is associated with petechiae around the mouth. The rash may precede the acute illness by days.

Within twenty-four to forty-eight hours after the onset of this illness, the patient becomes somnolent and may lapse into coma or become extremely restless and delirious with delusions and marked psychomotor activity. Convulsions also may occur. The profound stage of the illness lasts three to five days and is followed by a fairly rapid fall in temperature and recovery. During the acute illness, the patient often manifests extreme muscle tenderness and will resist the slightest touch. Even the bed covers seem to cause pain.

In milder cases, the sensorium is not involved, but the patient complains chiefly of hyperesthesias and paresthesias involving scattered areas throughout the body including the limbs, scalp, and even the mouth. Nuchal rigidity or somnolence may also comprise the only neurologic complaints.

Leukopenia, noted in most cases is characteristic of Colorado tick fever. In a number of instances, a mild spinal fluid pleocytosis is noted, with the majority of cells being mononuclears. The virus has been isolated from the blood in most reported cases.

Pathologic studies. The nervous systems of patients who have died of Colorado tick fever have not been studied. In Swiss albino mice infected with the virus, the cerebral hemispheres and cerebellum reveal widespread areas of mild inflammation and necrosis. Occasionally, mild inflammatory and degenerative changes are seen in the spinal cord

VII. Czechoslovakian Tick Encephalitis

Pearce Bailey

A COMPREHENSIVE REVIEW of the clinical neurologic manfestations, diagnosis, and treatment of the tick-borne encephalitides found in Czechoslovakia, including the massive epidemic that appeared during 1951 in Roznava, a little village in Slovakia, was presented in a recent paper (*Revue Neurologique*, 96:384-408, 1957) by K. Henner* and F. Hanzal. According to these authors, the Czech tick-borne encephalitides, which they claim have been identified both virologically and epidemiologically, should be grouped with the arthropod-borne encephalitides of Central Europe and probably are related to Russian spring-summer encephalitis but are less like louping-ill in sheep.

This presentation comprises a résumé of the original report by Henner and Hanzal as cited above.

Epidemiology and virology. In the 1948 epidemic, Czech encephalitis appeared in many of the forest areas throughout Czechoslovakia, and, in the epidemic of 1953, cases were reported in nearly all parts of the country, including the suburbs of Prague. The disease is caused by a filterable neurotropic virus, first isolated by Gallia. In man, the virus can be isolated from the blood during the early phase of the disease and from the cerebrospinal fluid later. The natural hosts are small mammals, especially the Muride group of rodents. The responsible vector is the tick, *Ixodes ricinus*, which thrives in the humid, shaded areas of the country and reaches maximum vitality in May and June.

The virus, which is conserved through the eggs of ticks from one generation to another, is transmitted by the bite of an infected tick or by the drinking of unpasteurized goat's milk containing the virus. There is some evidence, also, that the virus may be transmitted by the ingestion of infected ticks through the alimentary tract.

The neurologic studies of Henner and Hanzal were made on 288 patients. The viral etiology of Czech encephalitis had been established in 24 by neutralization tests of significant titer and in the other 264 by frankly positive complement-fixation reactions. To the series were added observations on many additional patients who exhibited the typical clinical picture but who lived in areas too remote for laboratory examinations.

The Henner and Hanzal report also includes clinical evaluations of 99 of 660 patients afflicted with encephalitis in Roznava during the epidemic of 1951.

General clinicopathologic features. The notable features of Czech encephalitis according to Henner and Hanzal are its diphasic evolution, its diffuse involvement of the gray matter of the brain and spinal cord, and its low mortality rate – only a few fatal cases have been reported and in each instance these patients were cachectic and of advanced age (70 to 80 years old). Postmortem examinations of these patients by Bednar, Finderland, and Fischer revealed a diffuse encephalitis in which the gray matter was more affected than the white matter. Inflammatory changes were observed in the motor cells of the cerebral cortex, medulla, cerebellum, brain stem, and cervical cord. The lesions were less conspicuous in the basal ganglia, hypothalamus, and inferior olive. There was a polioencephalitic neuronophagia, a pseudoneuronophagia, as well as glial proliferations and perivascular infiltrations.

The incubation period usually ranges between seven and fourteen days, but it can be as short as three days or as long as three weeks. In about 75% of cases, the disease proceeds through two phases. The first is one of a virusemia, while the second shows definite involvement of the central nervous system. The remaining 25% of the cases are abortive forms characterized by an unremitting course until the most severe stage of the illness is reached.

The first phase, which lasts four to six days (fourteen days at the most), usually begins

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with an elevation of temperature (38 to 39° C.), headache and listlessness, occasional gastrointestinal disturbances, back pains, feeling of heaviness in the legs, and joint and muscle pains.

In the more acute forms of the first phase, the tongue is dry and blanched, there is a catarrhal congestion of the nasopharynx, the spleen is slightly enlarged, and the liver may be nodular and sensitive to pressure. The blood sedimentation rate is slightly elevated, and there is a slight leukocytosis and albuminuria. The cerebrospinal fluid, however, always remains normal during the first phase. After the first phase, a considerable remission that lasts several days usually occurs; sometimes the patients even feel as though they are getting well. As a rule, however, during these remissions, patients continue to complain of some weakness and easy fatigability.

When the virus invades the central nervous system and the second phase of the disease begins, headache becomes the predominant complaint. The temperature rises rapidly to 40.3° C. or higher, accompanied by chills. The blood pressure often falls, and some patients even go into shock. Diplopia, photophobia, hyperacusis, ringing in the ears, and vertigo are common. With serious forms, delirium is frequent and coma may intervene; both are followed by retrograde amnesia.

Mental symptoms are almost always present, characterized chiefly by memory defects, disorientation, and inability to concentrate. Hyperirritability, emotional lability, and anxiety reactions may be present; yet optic illusions and auditory hallucinations are relatively uncommon. Sleep rhythm is almost always disturbed; most of the patients suffer from hypersomnia. Rarely, there is an inversion of sleep or intractable insomnia. Some patients will sleep the entire day, but they always can be aroused. Tremors are a constant finding, affecting the hands, chin, lower jaw, tongue, and less frequently the lower extremities. As a result, speech becomes tremulous and the patient cannot eat or drink without aid.

Clinical neurologic forms. According to the predominant symptomatology, Henner and Hanzal distinguish 3 clinical forms of Czech encephalitis: [1] meningeal; [2] encephalitic; and [3] encephalomyelitic. These develop in about half of cases as the second phase of the disease.

The meningeal form is characterized by a predominance of meningeal manifestations. Focal signs are absent and whatever cerebral symptomatology is present is diffuse and expressed as mental disturbances or as anomalies in the electroencephalographic tracings. Examination of the spinal fluid reveals a typical meningeal spectrum.

In the encephalitic form, meningeal signs invariably are present, but superimposed upon them are focal cerebral signs, indicating the presence of pathologic foci in the brain. In the encephalitic forms, both clinically and pathologically, gray matter is damaged considerably more than white matter. The focal cerebral syndromes vary from patient to patient, and their chronology may vary in the same patient as the disease progresses. Involvement of the cerebral white matter results in pyramidal signs of an irritative nature, usually evidenced by asymmetrical hyperreflexia. Clear-cut hemiparesis is rare; sensory disturbances are exceptional and transient.

In most cases of encephalitis, cranial nerve signs appear early and are extensively involved. Commonly affected are the first, the third (more frequently than the sixth), the seventh, and the eighth cranial nerves. The optic nerve is rarely involved. Paralyses of the ninth to twelfth cranial nerves, causing dysphagia and dysarthria, are usually mild and evanescent except in fatal cases, where these manifestations are pronounced right from the start.

Many patients complain of vertigo. Spontaneous lateral nystagmus is frequent and deviation of the arms, while holding them extended, or in Bárány tests, is usually in the same direction as the nystagmus. The same directional deviation applies when testing station and gait, especially when walking with the eyes closed. Vestibular tests are abnormal for a long time, even into convalescence.

Cortical syndromes tend to be pronounced at the beginning of the encephalitic form, but evidence of circumscribed cortical lesions, as, for example, jacksonian seizures or aphasia, are relatively rare. Psychotic episodes are quite exceptional. Involvement of subcortical structures is characterized by extrapyramidal syndromes, which may predominate early in cer-

tain patients and persist through convalescence. These extrapyramidal syndromes are marked by hypokinesis, rigidity, catalepsy, and often increased postural reflexes.

A cerebellar picture, sometimes well defined at first glance or later revealed by a systematic examination, is frequent. Hypermetria and adiadochokinesis usually are more pronuonced than hypotonia. These neocerebellar signs are apt to be asymmetric. For example, if the hypermetria is more pronounced on one side, then the adiadochokinesis is more pronounced on the other. The so-called cerebellar-extrapyramidal antithesis obtains in Czech encephalitis. For instance, an irritative lesion of the extrapyramidal system may imitate a classical cerebellar syndrome, or vice versa. In this respect, Czech encephalitis resembles the Russian spring-summer encephalitis and louping-ill of sheep and by the same token differs from polioencephalitis and poliomyelitis. Midbrain involvement manifests itself by a paralysis of convergence and by nuclear lesions of the oculomotor nerves.

In the encephalomyelitic form, both the gray and white matter are affected. Lesions of the gray matter are highly selective and are found 10 times more frequently in the anterior horn cells of the cervical segments (C_5 to C_7) than in the lower lumbar segments. The resulting paralysis of the upper extremities is of a flaccid, peripheral type. Among right-handed persons, the paralysis is more pronounced on the right side. In 28% of cases, paralysis of the neck muscles was associated with marked muscular atrophy and weakness, vasomotor and trophic skin disturbances, acrocyanosis, changes in skin temperature, sweating, and abnormal pilomotor reflexes. On rare occasions, small muscles of the hand (C_7 to C_8) were atrophied. Horner's syndrome on the side of the paretic limb was relatively frequent.

In 10% of cases of encephalomyelitis, the lower extremities were affected by a flaccid paralysis in which the iliopsoas and quadriceps muscles were weak and atrophied and the patellar reflexes were diminished or absent, depending on the intensity of the underlying inflammatory lesions. These paralytic phenomena ordinarily developed during the first days of the second phase of the disease and quickly reached their height. In a few patients, paralyses developed late, sometimes even after the patient had been discharged from the hospital.

In the acute stage of the encephalomyelitic form, objective sensory disturbances are diffuse, temporary, and peripheral in type. Hyperesthesia is a constant sign. Common subjective sensory complaints are paresthesias, numbness, and pins and needles sensation. When present, spontaneous pains are usually bilateral, but they do not correlate with the paralytic phenomena. The pain may be of radicular type or causalgic in nature.

These myelitic manifestations are almost always combined with symptoms of encephalitis.

Cerebrospinal fluid. According to Henner and Hanzal, the cerebrospinal fluid varies according to the phase of the disease. In the first phase, the fluid is usually normal. Rarely there is a slight leukocytosis or a slight albuminocytologic dissociation. In the second phase, the fluid may be clear or show a fibrin web and a moderate increase of pressure. The cells increase from a few dozen to as many as several hundred per millimeter. The ratio of polynuclears to lymphocytes is about 50 per 100. The globulin reaction (Pandy, Ross-Jones, Nonne Appelt) is usually slightly positive, except for the reaction of Weichbrodt, which is negative. Tests for albumin are quantitatively normal or just slightly elevated. Sugar and chlorides remain normal; the colloidal gold reaction may show a slight meningitic curve.

In the course of a few days, the character of the fluid changes. The number of leukocytes diminish while the plasmocytes become more numerous; the globulin reactions are frankly positive; hyperalbuminosis reaches a level that is double or triple of the normal count; and the colloidal gold reaction gives a typical meningitic curve.

These spinal fluid changes persist into convalescence, which helps distinguish Czech encephalitis from poliomyelitis. Moreover, a sudden exacerbation of the clinical picture during convalescence may again render the composition of the cerebrospinal fluid temporarily abnormal, with pleocytosis and hyperalbuminosis.

Examinations of the spinal fluid are indispensable for diagnosis and for observing the course of the disease. A lumbar puncture is essential at the time of hospitalization, at the

beginning of convalescence before the patient is discharged to his home, and at the time of any exacerbation. A single lumbar puncture suffices in the abortive form of Czech encephalitis; otherwise, the puncture should be repeated every five to six days. Observing these criteria, we have never found an aggravation of symptoms due to lumbar puncture. Moreover a lumbar puncture, as a general rule, has a therapeutic effect on the headaches, particularly in the first days of the neural phase. They should not be repeated too often.

Course and prognosis. Patients suffering solely from viremia, without involvement of the nervous system, do not as a rule require hospitalization. In most cases, several days in bed are enough. The meningeal forms, on the other hand, must always be treated in a hospital.

Encephalitic forms always are more serious and require more difficult and individual decisions. The amount of hospitalization required for mild cases is fourteen days, for more severe forms, over a month. Convalescence may be long, at least another month after the patient has been discharged from the hospital. Disappearance of fever does not preclude the possibility of a new outbreak of symptoms. Very often in the course of convalescence, there is a massive loss of hair. After convalescence, various pseudoneurotic complaints such as headache, disturbance in sleep, emotional instability, depression and anxiety, inability to concentrate, and abnormal sweating, may persist. Duration of Czech encephalitis and intensity of the affliction depend in large measure on the age and premorbid personality of the patient. Children recover more quickly than adults. Among old people, Czech encephalitis can be a dangerous disease.

In the encephalomyelitic form, the duration of convalescence is determined by the extent and severity of paralysis. Patients with the mildest form recover with proper treatment in a few weeks and, at most, in a few months. Patients with serious forms require a prolonged course of rehabilitation. The patients afflicted with serious paralysis in 1948 have remained invalids with considerable muscular atrophy and paralysis of the muscles affected (Erhart).

On the whole, life expectancy with Czech encephalitis is good, even though the prognosis must be guarded in very old and very young patients, especially if the period of coma exceeds twenty-four hours. The incidence of the disease also appears to be decreasing due to the development of greater collective immunity in the population since 1953. Henner and Hanzal, in their neurologic clinic, treated 203 patients in 1953, 23 patients in 1954, and 38 in 1955. The diagnoses were all confirmed by serologic tests. They believe also that the neurologic manifestations have become milder during the last two years (1954-55).

Treatment. Henner and Hanzal have developed methods of supportive treatment in all phases of the disease. Bed rest is an important prophylactic factor, serving as a defense against the development of more serious forms. Acutely ill patients and those with involvement of the meninges of the central nervous system should be kept in bed as long as these signs are observable, even if they are mild. During convalescence, the patient must still remain in bed the greater part of the day.

In the acute encephalitic phase, Henner and Hanzal administer penicillin or Aureomycin. They believe these antibiotics act as a prophylaxis against superimposed bacterial infections and protect against the development of new foci, even though they do not eradicate the old ones. Other supportive treatments that have been used are autotransfusions after irradiation with ultraviolet light; antihistamines; and intramuscular injections of convalescent serum. The last use is indicated more for prophylaxis than for therapy. Specific gamma globulin has been tried in a few cases.

For the treatment of cerebral edema, Henner and Hanzal recommend intravenous injections of hypertonic glucose with vitamin C. At the beginning of convalescence, a series of adrenocortical extracts are administered and in late convalescence, injections of hexamethylene-tetramine-diiodide-gelatinate (intradodia). The value of lumbar punctures for headache has already been mentioned. Mild forms of paralyses are treated with hot compresses according to the Kenny method; patients with more serious forms of paralysis and muscular atrophy are directed to a rehabilitation center at the beginning of convalescence.

Roznava encephalitis. Roznava encephalitis is probably a variant of Czech encephalitis and

of Russian spring-summer encephalitis. Henner and Hanzal, however, give it special attention, because of its peculiar epidemiologic aspects, its compact clinical picture, and the fact that it was studied by a team of specialists, representing several clinical and basic disciplines.

The epidemic of Roznava encephalitis appeared at the end of April and the beginning of May 1951 and affected over 660 persons in the neighborhood of Roznava, a little village of Slovakia. The illness may be monophasic or biphasic in its clinical course. The first phase appeared between April 20 and 28 as an influenza-like infection. The second phase, beginning May 5, revealed meningitic and encephalitic manifestations.

The incubation period, as fixed by the epidemiologists, ranged from ten to fourteen days. More than one member of the same family was often infected. There were no contact infections. All the patients examined had consumed raw goat's milk from a single central source. The vector was the tick which infected the goat's milk, and the virus of the tick then entered directly into the milk. Raska and others obtained a positive isolation of the virus from a patient during the first stage of the second febrile phase. Its power as an antigen was weak, and it immunized very badly in the guinea pig. But the serum fixed the complement with the virus of Czech encephalitis and of Russian spring-summer encephalitis up to a titer of 1:16.

In about half the patients, the reaction of the illness was diphasic. Clinical manifestations of the second phase were essentially those of meningoencephalitis. The patients suffered excruciating headaches, vomited, and had difficulties of vision and sleep (with a preponderance of hypersomnia). They also had diplopia, together with meningeal and cerebral symptoms. Examination of the cerebrospinal fluid indicated a slightly elevated pressure, a leukocytosis of several hundred cells per millimeter and an increase in the protein content. The colloidal gold curve was usually meningeal in type; more rarely it was meningoparenchymatous. The spinal fluid abnormality as a rule persisted for several weeks after clinical manifestations disappeared.

In their clinic in Prague, Henner and Hanzal gave careful neurologic examinations to 99 of the 660 patients. These patients were studied ten to twenty months after the appearance of the initial symptoms. At the time of the examinations, 61 of the 99 patients had no complaints. Adults were engaged in their previous occupations, and children were back in school. Massive loss of hair during the encephalitic period was reported by 52 patients.

By far the most frequent sequela was an extrapyramidal syndrome, which was evident in 80 of the 99 patients. It was reminiscent of that in patients who had recovered from the acute stage of epidemic encephalitis.

Electroencephalograms were made in 90 of the 99 patients. Of these, 43 were abnormal. Theta and sub-theta waves were present in the records of 21 patients; in the records of 15 patients, the theta waves, which had frequencies of about 6 per second, were combined with fast activity. The theta waves, though observable in all leads, were more accentuated in bifrontal leads. This fast activity, present in 38 patients, was considered to be unique. Beta rhythm was predominant in 23 patients; in 15 others it was synchronous with beta waves. The beta rhythm had a frequency of 15 to 20 per second, was of low amplitude, and often appeared as flat waves. In the group with high amplitude, the tracings were characteristic of barbiturate intoxication. In 3 patients, there were bursts of beta waves mixed with alpha activity, as seen with hypersomnia.

In summarizing their report of the total 660 patients, Henner and Hanzal conclude that there are important differences between Roznava and Czech encephalitis. The former is more definitely poliotropic and this poliotropism is selective, affecting only certain parts of the extrapyramidal system, the gray matter of the diencephalon, and adjoining structures at the base of the third ventricle. The disease strikes selectively but not massively the nuclei of the cranial nerves and the gray matter of the extrapyramidal system, especially the pallidum, but it spares the cerebral cortex, the cerebellum, and the red nucleus. Although more than 300 patients exhibited neurologic syndromes, the spinal cord was not involved in a single case, which was not an exceptional finding in Czech encephalitis. Moreover, in Czech encephalitis, the typical extrapyramidal

picture of Roznava encephalitis was found only in patients who had consumed raw goat's milk. Henner and Hanzal also indicate that Bardof and Strauss found accentuated extrapyramidal symptomatology in animals in which the infection was introduced through the gastrointestinal tract.

The gross lesions of Roznava encephalitis apparently are reversible. In the entire series there was not a single fatality. Nevertheless, the prognosis must still be guarded, because, as was demonstrated in epidemic encephalitis, a bitter day of deception often ensued after apparent recovery. Sometimes it came immediately after the acute phase, sometimes at the end of a year, but even as long as after fifteen to twenty years.

According to the authors, another important lesson learned from this study is the value of interdisciplinary collaboration between various clinical and basic specialists. The collaboration does not only concern clinicians but also epidemiologists, microbiologists, zoologists, parasitologists, hygienists, and doctors of veterinary medicine.

In these studies, neurologists were available to examine the patients both in the field and in the hospitals. The role of the neurologists, among the clinicians, was very great. It still happens too often that in a situation of this sort neurologists arrive too late or only after definitive sequelae have become established. Clinical neurologists should be important members of the research team, not only for the clinical descriptions, but to make important correlations that add much to our total knowledge.

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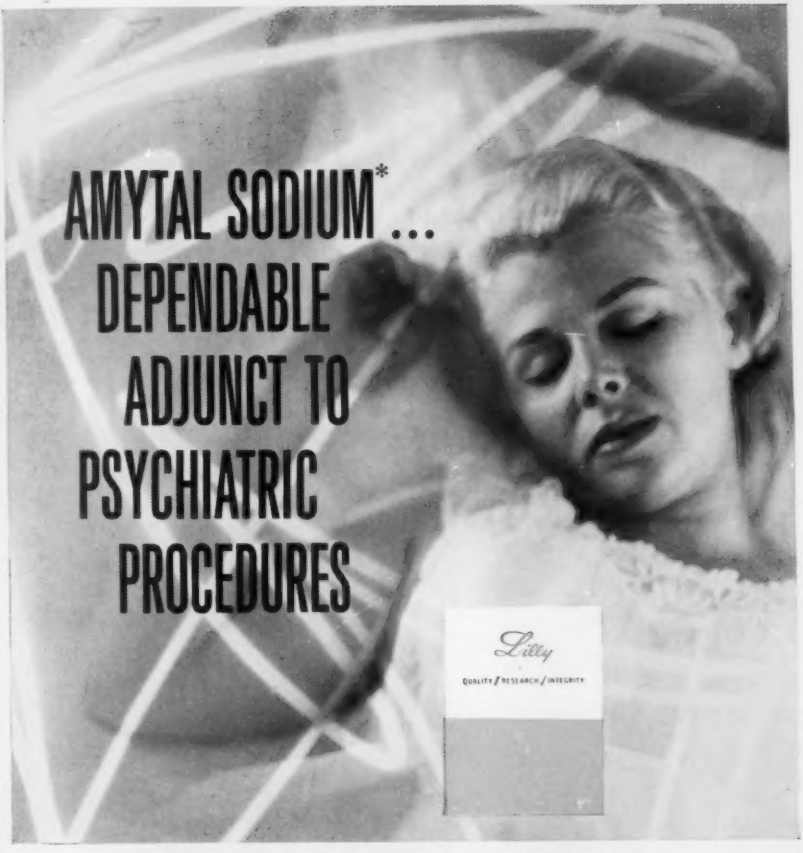

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NOVEMBER 1958

Deadline for AAN Sessions Is December 1, 1958

Monday, December 1, 1958, is the deadline for the submission of abstracts of papers for the scientific sessions of the 1959 annual meeting of the American Academy of Neurology, to be held at the Statler-Hilton Hotel, Los Angeles (April 16-18, 1959). All abstracts for papers-from-platform (150 word maximum) should be sent to the Scientific Program Chairman, Dr. Gilbert H. Glaser, Section of Neurology, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn. Abstracts for scientific exhibits and demonstrations (also 150 word maximum) should be forwarded to Dr. Louis D. Boshes, Department of Neurology and Psychiatry, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago 11.

International Myasthenia Symposium To Be Held at the 1959 AAN Meeting

To be held in conjunction with the annual 1959 AAN meeting in Los Angeles and under the joint auspices of the Myasthenia Gravis Foundation and the National Institute of Neurological Diseases and Blindness is the second International Symposium on Myasthenia Gravis[1] (April 18-19, 1959). The tentative program of the symposium, which will be chaired by Kermit E. Osserman, divides the scientific sessions into three parts. Following introductory remarks by Henry R. Viets, the first part is devoted to studies on the anatomy, biochemistry, and physiology of the normal and the myasthenic neuromuscular junction. The second part deals with the clinical aspect of myasthenia gravis, including discussions on epidemiology and genetics, on what is and what is not myasthenia gravis, and on factors contributing to exacerbations. The third part of the program, which concerns the drug management of myasthenia gravis, will highlight discussions on new anticholinesterase compounds, the use of the thymectomy and carotid sinus denervation, and the management of cholinergic crises. A summary of current trends in myasthenia gravis research will be given by George D. Gammon of the University of Pennsylvania. A corps of carefully selected national authorities on myasthenia gravis have been selected as participants in this symposium. Among the participants from abroad will be Albrecht and Elizabeth Struppler of Munich, Raymond Greene and I. Schrire of London, Nicoli Grashchenokov of Moscow, and Kurt Pateisky of

[1]The First International Myasthenia Gravis Symposium was held at the University of Pennsylvania, December 8-9, 1954.

Vienna.... Inquiries about the program should be sent to Dr. Kermit E. Osserman, Chairman Second International Symposium on Myasthenia Gravis, 4 E. 89th Street, New York City.

World Neurosurgical Group Schedules International Congress

The Administrative Council of the WORLD FEDERATION OF NEUROSURGICAL SOCIETIES has announced that the Second International Neurosurgical Congress will be held at the Statler Hotel in Washington, D. C. (October 14-20, 1961). This announcement was made by David L. Reeves, Editor of Transactions of the Federation. According to the tentative agenda, there will be a business meeting of the Federation's Executive Committee, composed of two delegates from each of the member societies, on Saturday, October 14, 1961. Registration will begin and an official reception will be given on Sunday, October 15; and the Scientific Sessions will be held from Monday, October 16 to Friday, October 20. All activities will be housed in the Statler Hotel.... The American Express Company has been selected as the official travel agent for the Congress. The travel agents have agreed to accept local currencies in payment for transportation to and from the Congress and within the United States and for hotel accommodations, rooms, and meals which have been arranged prior to departure for the Congress. These services will be negotiated at the offices and agencies of the American Express Company throughout the world.... Among the officers of the WORLD FEDERATION OF NEUROSURGICAL SOCIETIES are Paul C. Bucy, President; E. H. Botterell, Vice President; Bronson S. Ray, Secretary General; and Barnes Woodhall, Treasurer.... Further details about the Second International Neurosurgical Congress will be published from time to time.

Congressional Resolutions Favor International Medical Research

Joint resolutions introduced in the Senate (S. J. Res. 199--August 13, 1958) by Senator Lister Hill (Dem.--Ala.) and in the House (H. J. Res. 698--August 14, 1958) by Congressman John E. Fogarty (Dem., R. I.) call for the creation of a federally supported program in collaborative medical research on a world-wide basis. The broad purposes of the resolution envisage an international mobilization of medical science for a cooperative war against disease and as an effective instrument of peace.... Contained in the provisions of the resolution are measures to encourage and support the planning of international medical research, to award research and training grants to worthy projects and institutions abroad, and to encourage and support the rapid interchange of knowledge and information related to medical science. The program also authorizes the strengthening of the medical research activities of the World Health Organization and other international bodies.... The more specific language of the joint resolutions asks for the establishment of a National Institute of International Medical Research within the framework of the

National Institutes of Health of the Public Health Service, Department of Health, Education and Welfare.... The program would authorize the appropriation of $50,000,000 annually to be expended under the supervision of the Secretary of Health, Education, and Welfare chiefly through the U. S. Public Health Service, and, specifically, the National Institutes of Health.

Neurophysiological Week at the Salpetriere

The annual Neurophysiological Week was celebrated at the Salpetriere in Paris under the presidency of Professor Th. Alajouanine and the secretary-generalship of Antoine Remond. The central theme of the scientific sessions (October 20-25, 1958) was "sensory integration." After an introduction by Professor Alajouanine on the evolution of ideas on sensory integration in neurology, some 28 neurologists and neurologic scientists from France and other countries participated in the presentation and discussions. The sessions terminated with a summary of the proceedings by Auguste Tournay.

World Congress for Welfare of Cripples To Be Held in New York

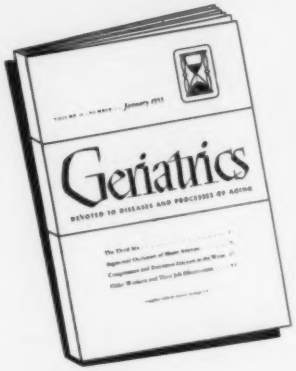
At the invitation of the National Society for Crippled Children and Adults, Inc., in Chicago, the Eighth World Congress of the International Society for the Welfare of Cripples will be held in New York City during the week of August 29, 1960. Tentative plans for the Congress, the first one to be held in North America, provide for a number of sessions devoted to neurologic disorders. Howard A. Rusk has been elected Congress president; Henry H. Kessler and Leonard W. Mayo are serving as co-chairmen of the Program Committee; and the secretary-general is Donald V. Wilson, International Society for the Welfare of Cripples, 701 First Avenue, New York 17, New York.

Sister Kenny Foundation Offers Research Scholarships

The Sister Elizabeth Kenny Foundation announces continuation of its program of postdoctoral scholarships to promote research in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowhip training in either basic or clinical fields concerned with the broad problem of neuromuscular diseases. Each grant provides a stipend for a five-year period at the annual rate of $5,000 to $7,000 a year depending on the scholar's qualifications. To be eligible, candidates must be from medical schools in the United States or Canada. Members of the Medical Advisory Committee on the scholarship program are T. B. Rasmussen, Oliver H. Lowry, H. W. Magoun, Irvine McQuarrie, H. Houston Merritt, Lewis Thomas, and C. N. Woolsey.... Inquiries about further details on the program should be addressed to: Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Inc., 2400 Foshay Tower, Minneapolis 2, Minn.

Briefs The German Society of Neurology met in Hanover (September 19-21, 1958). The meeting highlighted two central themes, polyneuritis and polyneuropathy and rehabilitation in neurology. Meeting conjointly was the German Multiple Sclerosis Society (September 20) and the German section of the International League Against Epilepsy (September 18).... The Tenth Western Institute on Epilepsy, sponsored by the Western Institute on Epilepsy and the University of Colorado School of Medicine, was held in Denver, Colorado, October 30-November 1, 1958.... Among the distinguished guest lecturers this fall at the National Institute of Neurological Diseases and Blindness were Professor Andrew F. Huxley of Cambridge, who revealed recent work on nerve impulse transmission (September 22); Sir John Carew Eccles, Professor of physiology at the Australian National University, who presented his recent work on synaptic excitatory and inhibitory action of the nerve cell; Professor Emeritus Archibald Vivian Hill of the University College, London, who gave a paper entitled "Today Physiology is Chemistry and Physics" (October 7); and Dr. Ernst B. Chain, Pharmacologist and Nobel Laureate, who lectured on "Recent Studies on Carbohydrate Metabolism in Muscle and Brain" (October 8).... A special issue of "Acta NEURO-Psychiatrica" will be published in honor of the sixtieth birthday of Professor Dr. Ihsan Sukru Aksel of Istanbul.... Robert A. Utterback of the State University of Iowa has accepted the post of Professor of Neurology at the University of Tennessee School of Medicine in Memphis.

Reese Bailey



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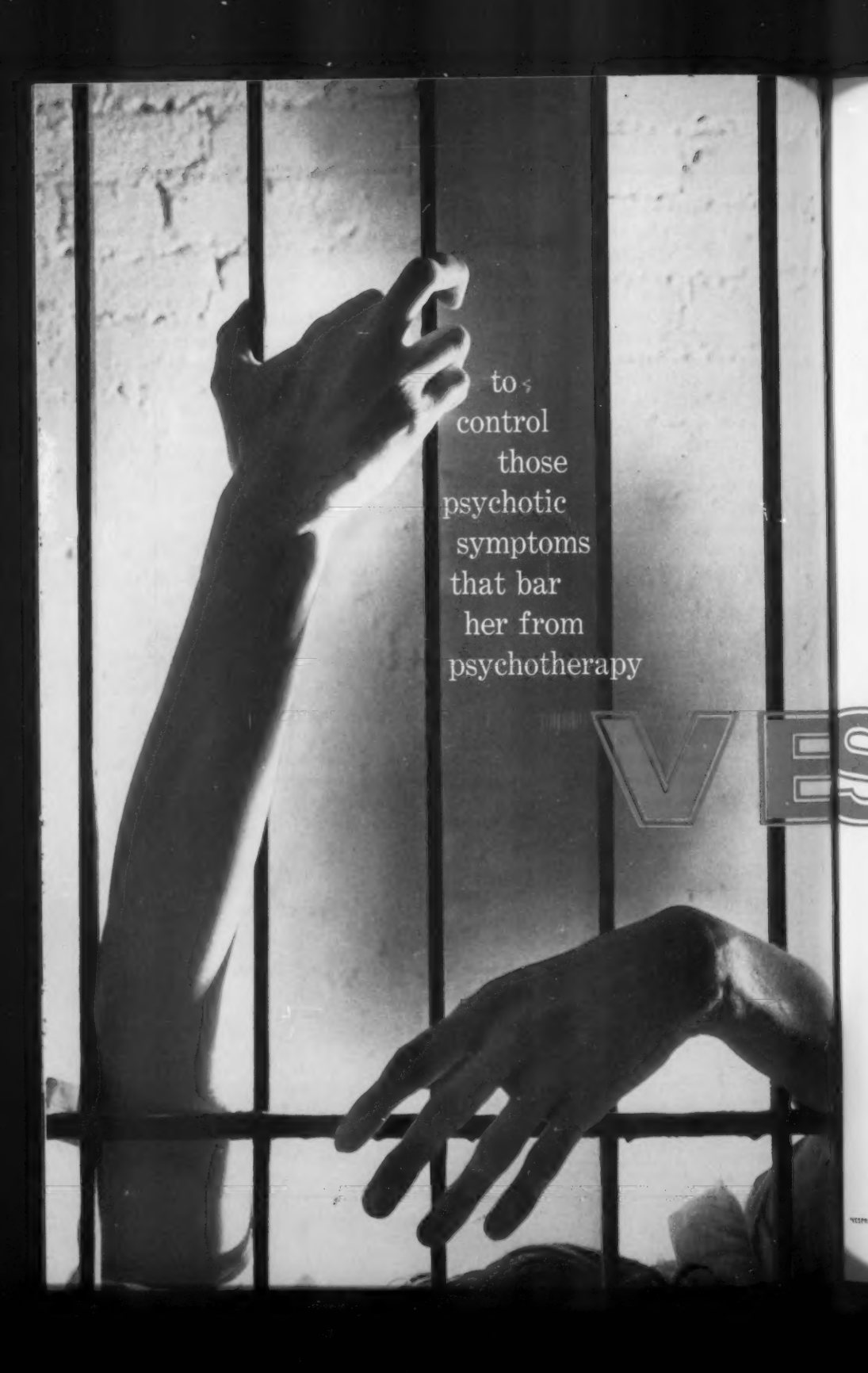
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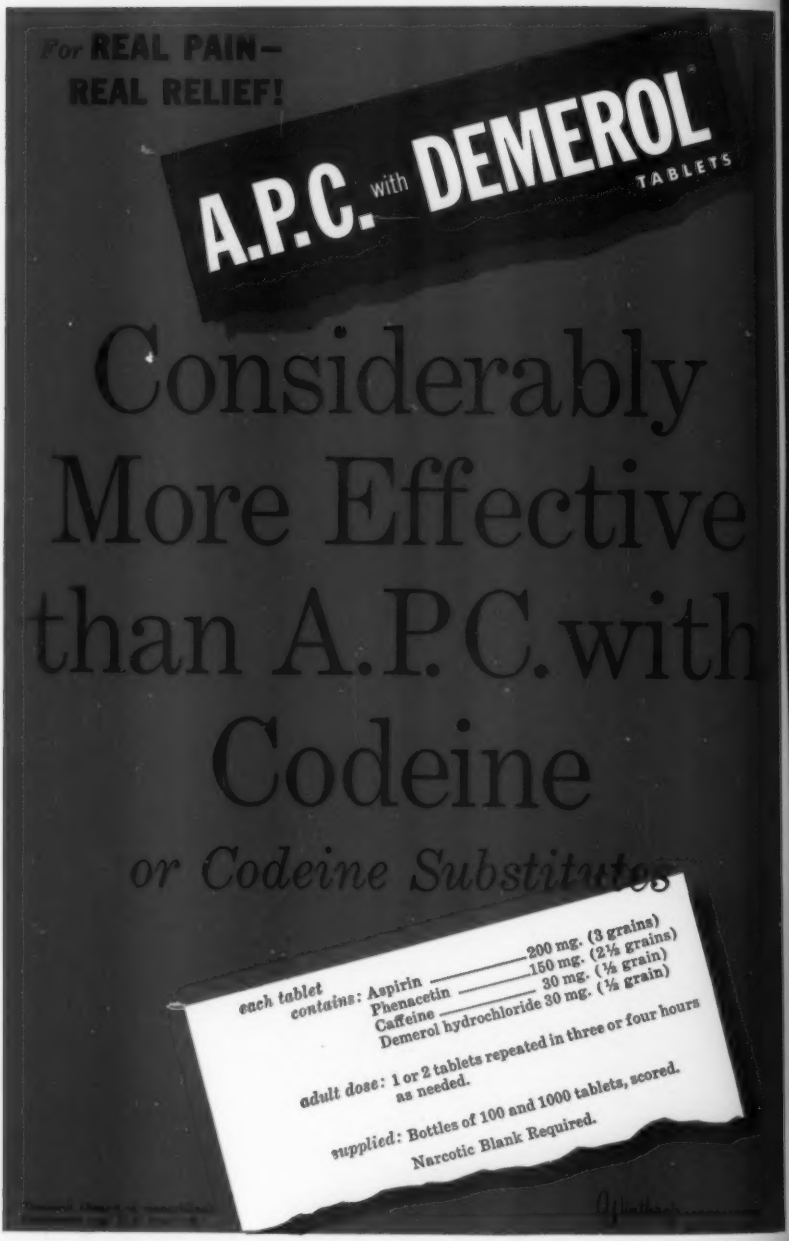
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